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THE HEALING OF CAVITIES.

By W. Pagel, M.D.,

PATHOLOGIST AND MEMBER OF THE RESEARCH STAFF TO THE PAPWORTH VILLAGE SETTLEMENT, CAMBRIDGE,

AND

F. A. H. Simmonds, M.A., M.B., D.P.H.,

MEDICAL SUPERINTENDENT OF THE MIDDLESEX COUNTY SANATORIUM, CLARE HALL, SOUTH MIMMS, ENGLAND.

(From the Sims Woodhead Memorial Laboratory Papworth Village Settlement, Cambridge, and the Middlesex County Sanatorium, Clare Hall, South Mimms, England.)

The importance of cavitation of the lung in pulmonary tuberculosis has long been recognized, though more recently increased attention has been given to this subject, stimulated by the use of active methods of cavity closure. Physiologic and pathologic studies support the view that the same processes are at work in healing cavities whether methods involving active collapse are used or if spontaneous healing occurs. The latter possibility was first recognized by Laennec,[4] whose knowledge was based on careful morbid anatomic studies. He thus describes the manner of cavity healing: "(*a*) Conversion of an ulcer into a fistula, lined, like all those which may exist without injuring the general health, by a membrane analogous to the tissues of the healthy body, or in another way (*b*) by means of a cicatrix more or less complete and consisting of cellular fibro-cartilaginous or semi-cartilaginous substance." Similar observations were made by Latham:[5] "In examining by dissection . . . . among many existing vomicæ we occasionally find the traces of a vomica healed. At the apex of the lung we find an indentation and descending from it for half an inch or an inch, a thick perpendicular line of tough ligamentous substance. Sometimes this substance, by being pulled asunder, is discovered to contain the remains of a cavity and sometimes not."

Such descriptions indicate that these observers recognized two methods by which a pulmonary cavity could heal; the cavity might become lined by a natural membrane, or the diseased area might be replaced by fibrous scar tissue.

Modern authors have also provided accounts of these modes of healing, although, compared with the abundance of clinical observations, full anatomic proof is surprisingly infrequent. Epithelialization and dense fibrosis of the cavity wall, following substitution of the local active tuberculosis by ordinary granulation tissue has been described by Pagel[7] (1932), Alexander[1] (1935), and Pagel and Robinson[9] (1936). The replacement of a cavity by a fibrous scar has been demonstrated by Sweany[11] (1935). In their patients the course of the lesions was traced radiologically and the healing demonstrated anatomically. Pinner[10] and, more recently, Marienfeld[6] (1938) aptly review the clinical and anatomic literature of this subject.

Can a cavity heal in any other way? We know that caseous lesions become inspissated and shrunken and that calcium salts commonly are deposited in these areas, and the radiologic appearances of such a quiescent lesion are familiar. Calcified foci at the site of a previously demonstrated excavation are sometimes mentioned in the literature, their development having been traced in serial skiagrams. Such a course was probably followed by the following illustrative case:

Case 1.—M. M., female, aged 34. Artificial pneumothorax was induced in June, 1931, when all zones of the right lung were involved. A definite cavity in the lung was reported and sketched several times. No calcification noted (film not available). Sputum 1 ounce daily, and tubercle bacilli present. Six weeks later expectoration had ceased; 4 months later pleural effusion followed the spontaneous rupture of an axillary adhesion. Complete apical collapse persisted and the displacement of the mediastinum to the left concealed the upper in the mediastinal shadow. With gradual obliteration of the pleural space, the upper lobe again became visible, and in 1938 an area of calcification is seen occupying the site of the former cavity (Fig. 1).

Proof of this process by postmortem section of the lung has been lacking up to the present, though Graeff[3] (1935) has recorded one example in which a cavity was filled by a homogeneous caseous mass which also obstructed the stem bronchus. Surrounding layers consisted of cells in various stages of destruction, with nuclear débris, and finally a capsule of fibrous tissue and collapsed alveoli. In the example next to be described, a system of cavities repeatedly demonstrated by skiagrams were found at autopsy to be replaced in a similar manner by caseous foci in which considerable *calcification* had occurred, and the lumen of the corresponding bronchi was completely filled by caseo-calcareous material.

Case 2.—L. F., female, aged 21, was found to be suffering from pulmonary tuberculosis in September, 1935. Left artificial pneumothorax was induced in November, 1935, and she remained at a sanatorium until August,

FIG. 6 FIG. 1

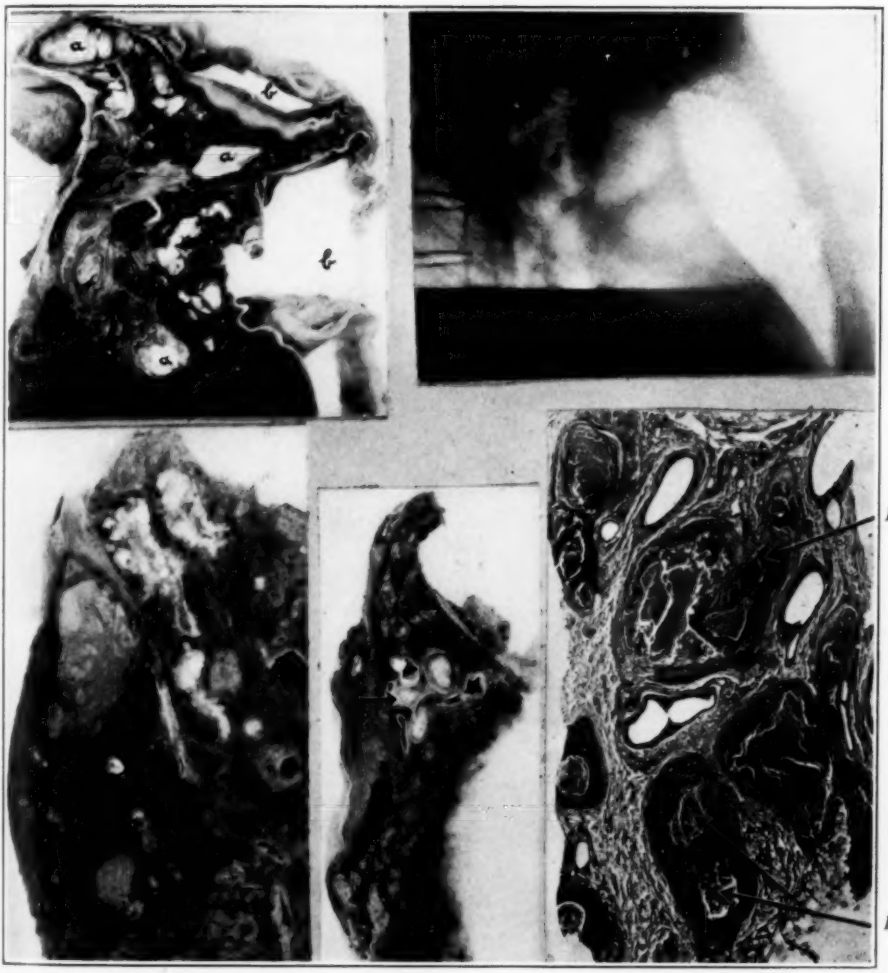

FIG. 10 FIG. 8 FIG. 7

FIG. 1, Case 1.—Calcification at site of former cavity. Fluid in pleural cavity.

FIG. 6, Case 2.—Survey of the left upper lobe. *a*, Caseous and calcareous foci at site of former cavities; *b*, artificial pneumothorax with broad adhesions.

FIG. 7, Case 2.—Histological survey of some of the old caseous and calcified nodules. *Bd*, *B*, occluded bronchi.

FIG. 8, Case 3.—Left upper lobe. Group of 3 bronchi filled with caseous material (arrow). Remains of ragged cavity below.

FIG. 10, Case 4.—Left lung. (See text.)

FIG. 2 FIG. 3 FIG. 4

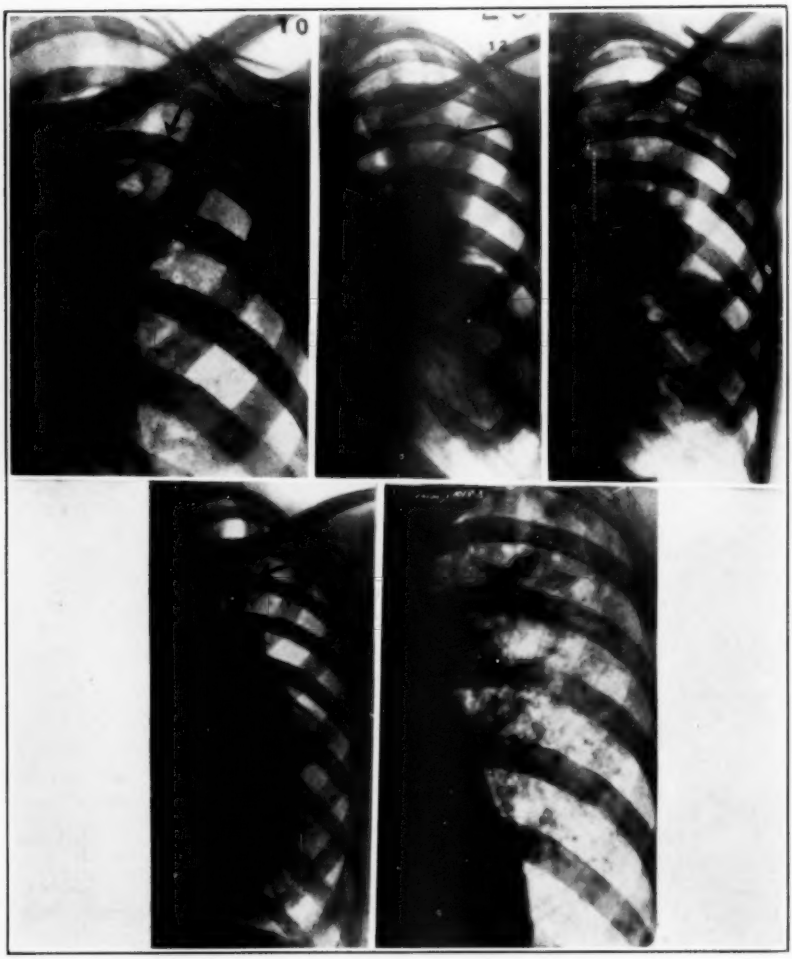

FIG. 5 FIG. 9

FIG. 2, Case 2.—System of cavities in the left upper lobe, October, 1935.
FIG. 3, Case 2.—Artificial pneumothorax. Cavity system still visible, December, 1935.
FIG. 4, Case 2.—Similar picture, April, 1936.
FIG. 5, Case 2.—Cavity system substituted by calcified nodules, December, 1937.
FIG. 9, Case 4.—Left lung. Circular shadows (cavity system?).

1936. No evidence of disease in the right lung was then noted and the tubercle bacilli present in the scanty sputum disappeared after a few months, but Roentgen ray showed that the shadows indicating a system of cavities in the left upper lobe persisted, and pleural adhesions were present in this region. Temperature and pulse normal, blood sedimentation rate 34/42 (Westergren). While attending as an out-patient for refills evidence of disease became obvious in the right upper zone, and she was admitted to Clare Hall. Temperature 97 to 98°, pulse 80 to 90, sputum scanty, tubercle bacilli present. Blood sedimentation rate 63/96. Division of adhesions on the left side appeared too difficult and dangerous. A pneumothorax was induced on the right side. Temperature 97 to 98°, pulse 120, R. 26. Three weeks after induction, the patient died shortly after a severe attack of dyspnea.

Postmortem Examination. Subcutaneous emphysema was present on the right side of the chest, and on opening the thorax, emphysema of the anterior mediastinal tissues was seen. On the *right* side there was very marked collapse of the lung, and numerous fine string and veil-like adhesions were found.

On the *left* side the lower half of the pleural cavity was obliterated, and stretching across the pneumothorax cavity from the upper lobe a broad band of tissue (1 inch diameter) was attached to the axillary region of the chest wall. No lesions were found in other organs.

After hardening in formalin, section of the *right* lung showed caseous lesions, in a few of which were small central areas of liquefaction, but no older cavities. Close to the apex there were a number of emphysematous bullæ (probably the fatal spontaneous pneumothorax and emphysema was due to the rupture of one of these).

Coronal section of the *left* lung through the broad adhesion showed marked thickening of the pleura. The upper half of the lung contained several old caseous and calcifying foci, and (Fig. 6) in particular in the broad adhesion there was a larger area of this nature occupying the site of the cavities seen in the earlier Roentgen ray films (Figs. 2 to 5). On microscopic examination, the obsolescent and partly calcified nature of these lesions was confirmed, and further it was clear that the bronchi to these areas were occluded by shrinkage and filling with caseous and calcifying material (Fig. 7).

Coryllos[2] (1933) and others have stressed the importance of obliteration of the bronchial lumen in the clinical healing of cavities. Kinking of the bronchus is suggested as the commonest cause, especially when some form of collapse therapy has been employed. Other factors must also be considered, and these include edema of the wall, tuberculous granulation tissue, fibrous stenosis and obstruction by a plug of caseous material. The last was probably the cause in the second case we have described; obliteration and obsolescence of the associated cavity, with the deposition of calcareous material in the inspissated cavity contents was the result.

The same process at an earlier stage is seen in the following case, where the findings resemble those described by Graeff, and illustrate again the changes which occur after closure of the draining bronchus.

Case 3.—Q. A., female, aged 17, 8 weeks after the operation of extrapleural pneumolysis (pneumothorax), developed an empyema of the extrapleural cavity, following rupture of a tuberculous cavity in the lung at the time of operation. The tear was repaired by oversewing. She died 4

months after the operation from secondary hemorrhage. At post-mortem examination the remnants of the cavity were found, and the tributary bronchi were blocked by caseous and mucoid material (Fig. 8). The lumen of the cavity was filled with an inspissated caseous mass rich in cholesterol crystals and lime salts. This drying-up of the caseous contents suggests that the earlier stages of healing had occurred, and were dependent on the closure of the draining bronchi. But there were, in this case, several lobular pneumonic foci in the neighboring lung tissue, the result of aspiration of infective material.

The clinical diagnosis of cavitation, though greatly advanced by radiologic methods, is beset by pitfalls. When disease of the bronchi or pleural fistula can be excluded, the expectoration of ½ ounce or more of sputum is strong indication of excavation in the lung, though cavities which provide no other clinical evidence owing to their very small size may, of course, yield mere traces of tuberculous expectoration. Ring-shaped shadows in the radiograph are also of obvious importance, especially with definite amounts of sputum, but caution should still be observed unless at some time a fluid level is seen in the suspected area. When an area of lung tissue has undergone an acute infiltration, a zone of leukocytic "precavernous demarcation" is found, which may show on a film as a nearly circular outline (Alexander, 1935). Should the process progress to caseation and the caseous material later be expectorated, this zone would become the granulating wall of a freshly formed cavity. Were such an area sectioned postmortem, it might superficially resemble the condition we have described above. Nevertheless, excavation has not yet occurred, and with due care it should not be confused with a healing cavity. The acute character of the process, the still-evident lung structure, the absence of calcification and of bronchial obstruction are important differences.

A different condition but perhaps not without affinity to this state of "precavernous demarcation" was seen in the following case, where the appearances on the radiograph had suggested a diagnosis of cavitation in the left upper zone.

Case 4.—F. B., male, aged 27, was a contact of his father, who had fibro-cavernous phthisis. He was ill for a few months with lassitude, slight cough and scanty sputum, which contained tubercle bacilli, later proved by culture to be of the human type. In February, 1938, temp. 98 to 100°; pulse 90 to 120; blood sedimentation rate (Westergren) 40/73, and Roentgen ray showed infiltration in the right upper zone, and in all zones of the left lung, where the appearances also suggested cavitation in the upper zone (Fig. 9). Artificial pneumothorax was induced, but failed to produce improvement. A severe enteritis set in, and caused death 2 months later.

Post-mortem examination revealed the extensive and very acute tuberculous enteritis, with gangrenous ulcers, which was the immediate cause of death.

Lungs. In the left upper lobe there are three caseous areas the size of a large walnut including the bronchi leading to the apex and the subapical parts (Fig. 10). The caseous substance is soft and faintly red. In the dorsal portion there is some old caseous tissue gray in color and of harder

consistency. The lung tissue surrounding the foci is atelectatic. In the apex of the lower lobe, which appears to be dislocated mesially and vertically there is an area the size of a small tomato consisting of the same soft caseous and reddish mass as the described lesions in the upper lobe. The bronchus leading to the focus is filled with the same mass. There are a number of smaller foci of the same kind throughout the lower lobe.

Histologic Examination. The foci in the upper and in the apex of the lower lobe are caseous areas in a state of wholesale liquefaction. Between the liquefied parts, however, are areas of still preserved caseous tissue with some remnants of elastic fibers and just recognizable alveolar structure. The remains of caseous tissue are surrounded by edematous fluid interspersed with innumerable leukocytes. Towards the thick fibrotic capsule of the foci the mass is more solidly caseous and contains patches of red blood cells and small vessels engorged with erythrocytes. The surrounding lung tissue is atelectatic, but not infiltrated.

Here there were a number of caseous lesions in a state of liquefaction. Because of the presence of red blood cells, especially in the central parts, this may be called "red liquefaction," which is due to a high degree of toxic and hypersensitive irritation of the vessels, described by Pagel and McCallum[8] (1935).

The histologic picture rules out the possibility that the foci were originally cavities filled by a blood clot, now changed in color by the breaking down of the red cells. It might have been expected that the lesions described would have caused some solid focal shadows in the radiograph. Two explanations suggest themselves. The first is that at the time of the film, a state of "precavernous demarcation" was present, and that the collapse by pneumothorax stimulated the production of a fibrous wall around the liquefying foci. Coryllos stresses the importance of pneumothorax in limiting the oxygen supply of the lung tissue and so stimulating fibrosis. But the areas under consideration showed a decreased density rather than an opacity to Roentgen rays. It is most probable therefore that cavities were present having very thick caseous walls, and that pneumothorax by kinking and blocking the bronchi, led to absorption of the contained air and approximation of the walls, so forming a solid caseous mass which began to liquefy.

The processes at work in the last 2 cases of this series therefore throw some light on the method of healing by calcification demonstrated in the second case.

Summary. The healing of active cavitation may follow one of three markedly different courses, namely:

(*a*) The ingrowth of an epithelial lining after the tuberculous disease has been replaced by ordinary granulation tissue and fibrosis.

(*b*) Approximation of the walls with the formation of a fistulous tract or of a strand of fibrous tissue if closure is complete, and

(*c*) Filling of the cavity with caseous material in which progressive calcification occurs.

Histologic and radiologic evidence is produced which is in agreement with this suggestion.

Such radically differing methods in the healing of cavities may be due to some difference in the origin and mode of formation of such lesions.

We wish to express our acknowledgments and thanks to Dr. J. Tate, County Medical Officer, Middlesex, for permission to publish these cases; to Dr. K. R. Stokes, Harefield, and Dr. St. G. Vaughan, Eversfield, for the loan and use of films and case histories (1 and 2), and to Drs. G. Gregory Kayne and A. G. Hounslow for their assistance.

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THE ANTIANEMIC EFFECT OF YEAST IN PERNICIOUS ANEMIA.*

By M. M. Wintrobe, M.D.,

ASSOCIATE IN MEDICINE, JOHNS HOPKINS UNIVERSITY MEDICAL SCHOOL, BALTIMORE, MD.

(From the Medical Clinic, Johns Hopkins Hospital, and the Department of Medicine, Johns Hopkins University.)

It has been the generally accepted opinion that "autolyzed" yeast possesses a factor which, after mixture with the gastric secretion of normal persons, produces a hematopoietic response when fed to patients suffering from pernicious anemia. According to this view, unless normal gastric juice is added, such an effect does not occur. This "extrinsic" or dietary factor, furthermore, is thought to be lacking in non-autolyzed yeast.

This report described the effects of the administration of non-autolyzed yeast to 23 patients suffering from pernicious anemia.† The study was commenced when it was found that animals, given a diet supposedly lacking in "extrinsic factor"[27] failed to develop macrocytic anemia. Each of the constituents of this diet, which included brewers' yeast, was consequently tested for antianemic value. When this yeast, administered to a case of pernicious anemia in amounts corresponding to those given the animals, was followed by a well-marked hematopoietic effect, experiments were carried out with the purpose of answering the following questions: How regularly will the oral administration of yeast cause a hematopoietic

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† A preliminary report of these studies was presented at the meeting of the American Society for Clinical Investigation, in Atlantic City, May 2, 1938 (Abstract in J. Clin. Invest., **17**, 501, 1938).

response in cases of pernicious anemia? Will preliminary mixture of yeast with normal gastric secretion produce a substance which has greater antianemic value than yeast alone? Does the antianemic effect of yeast depend on persistence of intrinsic factor in the gastric secretion of the patient? What is the nature of the yeast substance and what is its relation to the antianemic principle contained in liver? The following experiments were carried out with the object of answering these questions.

Review of Literature. Interest in the antianemic value of yeast was originally aroused by certain points of similarity between the water-soluble vitamins and the antianemic principle[8,10a] or its precursor, the "extrinsic factor,"[23] as well as by Wills' description[26] of a type of macrocytic anemia in India which she considered to be due to a vitamin deficiency. This tropical anemia, she found, could be treated effectively by marmite, an autolyzed yeast concentrate.

Probably because of Wills' experience, in the trials which were made in cases of pernicious anemia, autolyzed yeast ("marmite," "Vegex") received almost exclusive attention and very few studies were made of the antianemic value of non-autolyzed yeast or of extracts which could be given parenterally. The reports concerning the value of autolyzed yeast were by no means in agreement. Goodall[12] found marmite in doses of 45 to 150 gm. definitely effective when fed in 3 cases of pernicious anemia and recorded less convincing data regarding a number of other cases. Ungley[24,25] also observed good hematopoietic responses in several cases and an alcohol extract of marmite, given daily in amounts derived from 120 gm. produced a good response in 2 cases. Connery and Goldwater[9] concluded that Vegex (6 to 24 gm. daily) may excite a reticulocyte response in cases of pernicious anemia, but the increases they record are small.

Using small amounts (12 gm. daily), Strauss and Castle[23] found Vegex and an alcohol extract of this substance ineffective when given alone, but a well-marked hematopoietic response followed preliminary incubation with gastric juice. The experience of Groen[13] who used 24 to 36 gm. of marmite daily was the same, whereas the Lassens[17] found their autolyzed brewers' yeast (12 to 20 gm. daily) ineffective even after incubation with gastric juice.

Davidson found marmite of no value whatever in 3 of his first 4 cases[10a] and only in 2 out of 12 additional cases reported later[10b] did a satisfactory hematopoietic effect result (34 to 90 gm. were used daily). It is noteworthy in considering Davidson's failure to demonstrate antianemic value in marmite in 13 cases, that in 2 of these cases a response to liver had already occurred, in 4 treatment by the use of liver was also not followed by the customary response, and in 3 cases the ineffectiveness of marmite by mouth was compared with the value of liver administered parenterally. Only in 4 of the cases in which marmite had failed was it shown that liver by mouth was effective.

As already mentioned, non-autolyzed yeast has received little trial in the treatment of pernicious anemia. Cohn, Minot, Alles and Salter[8] stated, in 1928, that no response was obtained in 1 patient given 120 gm. of yeast cake daily for 8 days, nor were 51 gm. of a yeast extract effective in another case. Slight improvement followed the administration of 10 gm. daily of a vitamin extract derived from yeast together with 90 cc. of an extract of wheat embryo. Ungley[24] used dried yeast (Yestamin) in 1 case only. The response was poor, but neither was marmite nor liver followed by an adequate response.

Russell[21] gave dried brewers' yeast (Harris) (about 12 to 24 gm. daily) to 4 patients. In 2 a moderate reticulocytosis followed, but the increases subsequent to the injection of liver extract were more than twice as great. In the remaining 2 cases, the reticulocyte change associated with the ingestion of yeast was insignificant, although in 1 of these patients the erythrocyte count increased nevertheless.

Spies, Payne and Chinn[22] gave 3 patients suffering from pernicious anemia an incubated mixture of normal gastric juice and 50 gm. autoclaved brewers' yeast (Harris) daily for 10 days. Two other patients were given the same amount of yeast after incubation with pepsin and trypsin instead of gastric juice. No change in the blood of any of these 5 patients occurred. This treatment was followed by the intramuscular administration of liver extract, which produced a characteristic response.

Ungley reported[24,25] that alcohol extracts of fresh yeast caused definite although moderate reticulocyte responses in 3 cases of pernicious anemia and in 1 instance a marked reticulocytosis occurred. In each of these cases, the subsequent oral administration of liver extract was followed by a greater effect than had been produced by the yeast extracts. In another patient an extract of yeast made by a method used in liver extraction caused only a slightly response. This patient, however, did not respond readily to liver by mouth.

It is of interest that in 1 of Ungley's cases above mentioned, an extract of autolyzed yeast was no more effective than that derived from fresh yeast. On the other hand, in another patient, an alcohol extract of marmite caused a well-marked reticulocytosis whereas "vitamin B_2 concentrates" derived from an aqueous extract of fresh yeast, produced less marked reticulocytosis.

Aqueous as well as alcohol extracts of 60 to 70 gm. of yeast were inactive, even after incubation with gastric juice, in 4 cases reported by Groen.[13] Lassen and Lassen[17] noted a very slight response in 2 out of 3 cases treated with a yeast extract which had been incubated with normal gastric juice.

Only Ungley[25] has reported on the use of yeast preparations parenterally. An alcohol extract derived from 27 to 48 gm. fresh yeast was given daily to 2 patients, a lead acetate fraction to 1, and an extract made by a method used for liver extraction to another. The last extract, given in amounts derived from 100 gm. daily, caused a very slight increase in reticulocytes and the erythrocyte count did not change. This patient, it may be noted, improved only slowly on liver therapy. The other extracts above mentioned caused no change in the blood when they were given parenterally although, as already mentioned, they had some beneficial effect when given by mouth.

In summary, a survey of the literature indicates that autolyzed yeast has been shown to have been effective in causing a hematopoietic response in about one-third of the cases of pernicious anemia in which it was tested, when amounts of 45 gm. or more were used daily. Several investigators have shown that smaller quantities are effective after incubation with gastric juice. As regards non-autolyzed yeast, it seems to have been tacitly assumed that it does not possess antianemic potency. Actually, however, trials have been reported in a few cases only, and in a number of those in which such treatment failed, the test was not altogether satisfactory or the amounts used were small. An important oversight in many of the experimental studies reviewed, is the failure to determine, when yeast was ineffective in causing a hematopoietic response,

whether liver or liver extracts, likewise given *by mouth*, were effective. Very often parenteral therapy was resorted to and the possibility of failure of absorption through the gastro-intestinal tract was completely ignored. The equivocal results following the use of extracts of yeast are inconclusive, for to assume that an extract is necessarily representative of the yeast as a whole is not justified.

Material and Methods. These observations have been made in patients whose clinical history and physical and laboratory findings fulfilled all the usual criteria required for the diagnosis of classical pernicious anemia. Achlorhydria, even following the injection of histamine, was present in each. All patients studied on the wards of the hospital were given a diet free of liver, kidney, brain and meat and in the majority the diet also lacked eggs. Except in the 1 instance which will be mentioned, as far as we were able to ascertain, the diet of these patients before coming to the hospital, had not been deficient. The observations have been summarized in Table 1 and are illustrated in the various figures. In the descriptions of the cases, only complicating diseases are mentioned. Details regarding history and physical findings are omitted for the sake of brevity.

The patients studied in the dispensary were asked to take no liver or other food or medication which is known to cause hematopoiesis in cases of pernicious anemia. It is believed that they adhered to these instructions.

It should be pointed out that all cases of pernicious anemia available for study were used as they appeared, *no selection of favorable cases* being made.

Three brands of yeast have been used: 2 of these (N, M) are known as "brewers'" yeast, while 1 is a "bakers'" yeast (F). Except in the one instance so indicated (M[w]), the yeast was in the form of a dry powder sold for nutritional purposes. In such powders the yeast cells are dead.

Yeast "N" is derived from a strain of *Saccharomyces cerevisiæ* and is grown on a carefully selected medium free of meat, kidney, stomach, liver or egg preparations of any kind. Autolysis is not allowed to occur. Nothing is added to the yeast powder. This yeast is said to contain about 12 to 13 international units of B_1 and 13 Sherman and Borquin units of "G" per gram. The "protein" content ($N \times 6.25$) is 45.3%.

Yeast "M" has been accepted by the Committee on Foods of the American Medical Association.[1] "The yeast is cultivated by inoculating a sterilized wort containing dextrose, sucrose and raffinose of molasses and other vegetable products and nutriments of organic and inorganic origin, with a pure culture of *Saccharomyces carlsbergensis*." The fermentation is carried on in a filtered air atmosphere and is much slower than for aërated bakers' yeast. The yeast is centrifuged and washed several times and then it is spray dried. The temperature attained by the yeast in the process of drying is less than 100° C. and probably not more than 70° C., and the heating time is probably less than 30 seconds. The protein content is 48%; carbohydrate, 39%. Each gram is said to contain at least 25 international units of B_1 and 42 Sherman units of G.

The above yeast was also obtained before drying as a filtered wet yeast (Mw) and in this form was given to 1 patient (M. Th.).

The bakers' type yeast (F) used in these studies is grown in a molasses and grain wort. It is a strain of *Saccharomyces cerevisiæ* grown rapidly at a higher temperature than the brewers' yeast. It is dried on a drum drier. It is said to contain approximately 160 international units of B_1 and 20 to 25 Sherman units of G per gm. of dry yeast. The protein content is 49.5%, carbohydrate about 29%.

Various extracts of these yeast powders were made for oral and parenteral use. One, "Yeast Ext. al.," was a 65% alcohol extract as described by

Ungley.[24] It was so diluted that 1 cc. of extract represented 1 gm. of yeast. Yeast extract "P.D." was prepared from yeast N by making a thick paste with water, freezing this and subsequently suspending the frozen mass in water. This was allowed to stand about 18 hours, the solids were then removed by centrifugation and the liquid dried in a vacuum drier at a temperature of 150° F. or less. The dried material was milled. The weight of the extract was 11.25% of that of the original quantity of yeast used.

Yeast extracts for intramuscular injection were made by 2 different methods. Extracts Y_1, Y_2 and Y_3 were made in the same way as liver extract is made, the main steps of the procedure being digestion of the yeast with N/5 sulphuric acid, extraction with water at a temperature of 85° C., concentration *in vacuo*, precipitation with alcohol (70%) and finally solution of the precipitate in water. Extract Y_L was made according to the insulin process in which preliminary extraction is made by means of an acid-alcohol solvent rather than with acid and water.

The "double" reticulocyte method for assaying antianemic substances in cases of pernicious anemia was used.[19] After a preliminary period of observation on a diet containing no recognized antianemic factors, the substances to be tested were given daily in successive periods of about 10 days' duration, a substance expected to produce no or little effect being given first and the (probably) more potent substance being given next. If the second substance is more potent than the first an increase in reticulocytes will occur, even though the first has already caused reticulocytosis. The magnitude of the second reticulocytosis as compared with the first and the effect on the number of red corpuscles, indicate the relative potencies of the two substances. If the first substance has already produced a maximal effect, no secondary reticulocyte rise will occur. By giving a number of different test substances in suitable order, comparison can be made in the same patient of the effectiveness of a variety of antianemic agents.

In some of the patients, for various reasons concerned with the health or pleasure of the patients, the test periods were not as long as theoretical considerations would have made desirable. In a few, the preliminary period of observation before test substances were given, was short. In others, administration of the substances assayed was unavoidably irregular. Again, in some cases it was not possible to compare the effectiveness of yeast given by mouth with that of liver given by the same route. Finally, in several patients, the presence of complications inhibited their response.

TABLE 1.—SUMMARY OF RESULTS OF ASSAYS IN CASES OF PERNICIOUS ANEMIA.

LEGEND FOR TABLE 1.

The table should be read from left to right. In most of the patients there were only 3 periods of assay. When there were more than this number of periods, the 4th, 5th and 6th will be found below the first three, and the 7th, 8th and 9th under the second three.

In the "Day of peak" column, the day given is that on which the highest reticulocyte count which followed administration of the substance assayed, was found. The number in parentheses indicates the total number of days of observation up to the time of this reticulocyte count.

Legends: "i.m." refers to intramuscular administration; "G. J." refers to normal gastric juice; "Y. E." to yeast extract; "L. E." to liver extract; "B. M." to beef muscle; "D. H. St." to desiccated hogs' stomach.

Full details regarding the various kinds of yeast and the yeast extracts are given under "Material and Methods."

Liver Extract "343" is the powdered liver extract for oral use manufactured by Eli Lilly & Co.; Liver Extract "L" is the extract (unconcentrated) of the same manufacturers for parenteral use. Liver Extract "W" is that marketed as Campolon by the Winthrop Chemical Company. Liver Extract "Le" is that made by Lederle, Inc. Liver Extract "J.H.H." is an extract made by ourselves from Lilly Liver Extract 343 and prepared for parenteral use. Full details are given in the individual case histories.

TABLE 1.—SUMMARY OF RESULTS OF ASSAYS IN CASES OF PERNICIOUS ANEMIA.

Patient.	Age.	Sex.	Weight, kg.	Period One.									Period Two.								Period Three.							
				Substance assayed.	Amt., gm. or cc.	Route.	No. of days.	R. B. C.s.		Retic., %			Substance assayed.	Amt., gm. or cc.	Route.	No. of days.	R. B. C.s.		Retic., %			Substance assayed.	Amt., gm. or cc.	Route.	No. of days.	R. B. C.s.		Retic., %		
								Initial.	At end of period.	Initial.	Highest.	Day of prak.					Initial.	At end of period.	Initial.	Highest.	Day of prak.					Initial.	At end of period.	Initial.	Highest.	Day of prak.
C. B.	59	F	60	Yeast N	104	Oral	10	2.90	3.19	0.1	**12.1**	9th (13)	Yeast N	120	Oral	29	3.19	4.14	6.4	1.2	... (44)								
E. R.	69	F	75	Yeast N	168	Oral	10	1.90	2.77	1.0	**15.8**	5th (16)	Yeast N + G. J.	150 150	Oral Oral	11	2.77	3.15	6.0	4.1	6th (27)	L. E. J.H.H.	3	i.m.	10	3.21	3.75	1.9	1.8	2d (40)
B. A.	43	F	44	Yeast N	44	Oral	11	1.81	2.26	2.6	**7.0**	6th (29)	Yeast N + G. J.	44 150	Oral	10	2.26	2.51	3.0	5.8	5th (39)	Yeast N + G. J.	44 150	Oral	12	2.51	2.95	2.8	3.0	10th (54)
G. Y.	68	M	64	B. M.	200	Oral	14	1.30	1.33	1.2	2.4	5th (7)	Yeast N	96	Oral	48	1.33	4.16	1.4	**27.3**	10th (26)									
C. V.	60	M	70	B. M.	200	Oral	15	1.81	2.43	2.8	**9.7**	9th (12)	Yeast M	125	Oral	10	2.43	3.31	2.0	**6.2**	7th (25)									
S. B.	57	F	66	B. M. $FeSO_4$	200 1.2	Oral Oral	14	1.86	1.75	0.2	2.2	12th (24)	Yeast F	99	Oral	9	1.75	1.92	2.2	**5.4**	6th (34)	L. E. 343	24	Oral	6	1.92	2.32	3.6	3.8	5th (41)
Period 4				L. E. W	10	i.m.	3	2.32	3.68	2.4	**16.6**	6th (48)																		
M. K.	45	M	80	B. M.	200	Oral	7	1.97	2.08	0.4	2.8	4th (150)	Y. E. Y_L	4	i.m.	7	2.08	1.57	1.2	2.4	3d (156)	Y. E. P.D.	64	Oral	8	1.57	1.81	2.0	**6.6**	7th (168)
Periods	4,5	&	6:	Yeast N	115	Oral	8	1.81	1.74	6.4	6.6	8th (177)	L. E. 343	12	Oral	10	1.54	1.86	6.6	6.6	4th (181)	L. E. W	5	i.m.	10	1.86	3.12	2.6	**23.4**	5th (192)
J. M.	67	M	52	B. M.	200	Oral	10	1.91	1.91	0.8	2.0	8th (14)	Yeast M	26	Oral	9	1.91	1.89	0.8	1.6	6th (22)	Y. E. Y_3	3	i.m.	10	1.89	1.75	1.2	**12.3**	5th (36)
Periods	4,5	&	6:	Y. E. Y_2	6	i.m.	8	1.75	1.90	0.6	**5.4**	12th (54)	Y. E. al.	77	Oral	20	1.90	2.14	1.8	**4.2**	5th (57)	Yeast F	81	Oral	5	2.14	2.37	1.2	1.8	4th (77)
Periods	7 &	8:		L. E. 343	12	Oral	10	2.37	2.04	0.6	**5.3**	7th (89)	L. E. L	3	i.m.	10	2.59	3.74	4.8	**6.4**	6th (98)									
L. D.	65	F	72	D. H. St.	19	Oral	14	1.04	1.22	4.4	**15.3**	7th (9)	Y. E. Y_1	3	i.m.	2	1.30	1.11	4.0	**9.4**	5th (27)	Yeast M	72	Oral	40	1.05	4.07	2.9	**19.6**	7th (43)
M. Th.	38	F	50	Y. E. Y_1, Y_2	3	i.m.	21	2.64	2.05	0.2	2.1	3d (8)	Yeast M(w)	80	Oral	10	2.05	2.00	1.4	2.4	6th (32)	Yeast M	50	Oral	10	1.78	1.90	0.8	**4.2**	7th (53)
Periods	4,5	&	6:	Yeast N	50	Oral	13	1.90	2.26	2.2	**7.8**	7th (63)	Yeast N	100	Oral	33	2.26	1.80	6.8	1.8	10th (79)	D. H. St.	30	Oral	49	1.80	3.49	1.0	**14.2**	8th (116)
M. T.	68	F	73	Y. E. P.D.	30	Oral	10	1.64	1.63	0.4	**3.8**	10th (17)	Yeast M	54	Oral	10	1.63	1.50	3.8	5.0	5th (22)	Yeast M	80	Oral	16	1.50	1.60	2.8	**7.8**	10th (37)
Periods	4 &	5:		L. E. 343	12	Oral	10	1.40	1.52	5.8	**9.2**	5th (50)	L. E. W	5	i.m.	10	1.52	2.07	1.6	**11.4**	7th (62)									
L. B.	46	F	50	Y. E. P.D.	17	Oral	10	1.04	1.03	7.4	5.1	8th (15)	Yeast F	75	Oral	9	1.03	0.94	4.0	4.6	8th (26)	Yeast N	75	Oral	8	0.94	0.98	3.6	**10.4**	6th (33)
Periods	4,5	&	6:	L. E. 343	12	Oral	10	0.98	1.29	5.2	**21.8**	6th (42)	Y. E. Y_L	5	i.m.	10	1.29	1.22	5.4	6.0	3d (52)	L. E. L	5	i.m.	10	1.22	2.40	2.2	**14.6**	7th (67)
L. E. S.	72	M	60	Yeast F	90	Oral	10	1.16	0.93	0.8	1.6	10th (18)	Yeast M	90	Oral	21	0.93	1.58	1.6	**13.4**	9th (27)	L. E. Le	1.2	i.m.	11	1.58	2.34	3.0	**13.3**	6th (45)
J. Mc.	61	M	60	Yeast F	90	Oral	21	3.40	3.57	0.4	4.6	20th (26)	L. E. 343	12	Oral	9	3.57	3.22	4.4	6.2	5th (34)									
E. G.	58	M	55	Y. E. Y_2	5.4	i.m.	10	2.18	1.66	0.8	0.8	6th (48)	Y. E. al.	80	Oral	7	1.88	1.76	1.2	1.2	5th (59)	L. E. J.H.H.	2.3	i.m.	10	1.76	2.88	0.8	**15.2**	8th (69)
Periods	4,5	&	6:	Yeast F	84	Oral	10	3.31	2.77	0.4	**4.4**	7th (215)	Yeast M	126	Oral	21	2.77	2.87	2.6	2.2	5th (224)	L. E. 343	16	Oral	7	2.87	2.65	1.8	**3.8**	8th (234)
Periods	7 &	8:		L. E. 343	24	Oral	9	2.65	2.81	2.4	3.2	5th (238)	Whole liver	230	Oral	12	2.81	3.48	2.4	1.2	5th (249)									

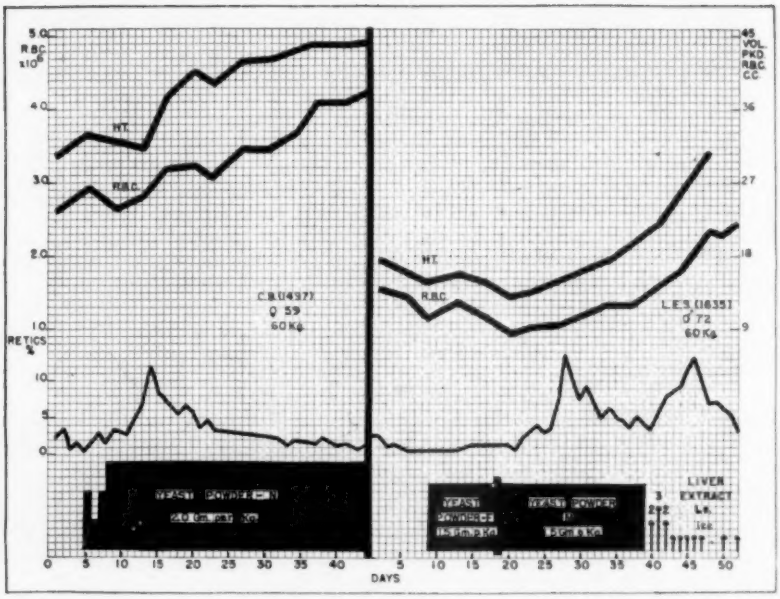

FIG. 1.—At the left, Patient C. B., showing hematopoietic effect of dehydrated brewers' yeast; at the right, Patient L. E. S., showing ineffectiveness of bakers' yeast, effectiveness of brewers' yeast. Ht refers to volume of packed red cells; R.B.C., to red cell count. In this and in the subsequent figures, these values are so plotted in relation to one another, that, when there is macrocytosis, the Ht value appears above that for R.B.C. and when the mean size of the red cells is normal the two lines coincide. Oral therapy is indicated by blocks, parenteral treatment by arrows.

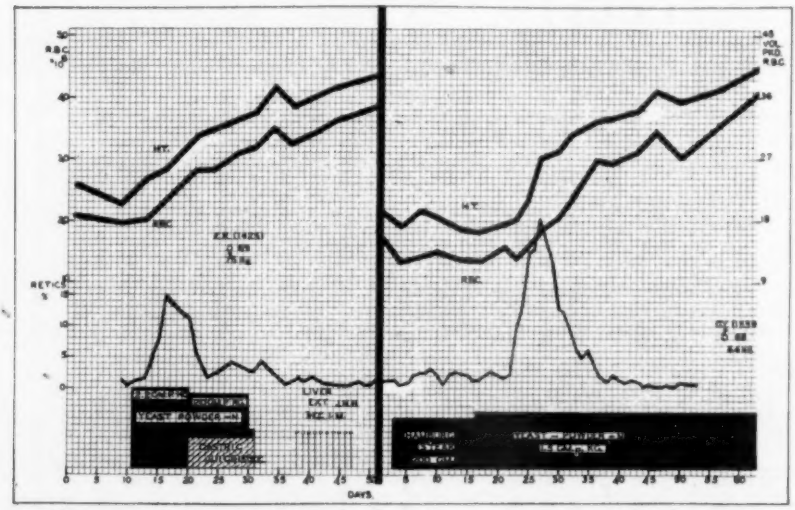

FIG. 2.—At the left, Patient E. R., showing maximal antianemic effect of brewer's yeast and the absence of a greater effect following administration of a mixture of this quantity of yeast with gastric juice from normal persons; at the right, Patient G. Y., showing lack of response to "extrinsic factor" (beef muscle), maximal response to brewers' yeast.

These defects in the clinical assays were unavoidable, but they are pointed out because they have a bearing on the interpretation of the results.

Results. *Dehydrated yeast powder caused rapid hematopoiesis in doses of 2 gm. per kg.* C. B. (No. 1497) (Fig. 1, left), 4 days after admission, was given brewers' yeast powder (N) in doses of 1.3 gm. per kg. body weight the first day, 0.7 gm. the second, 1.3 gm. the third, and 2 gm. per kg. in the succeeding 36 days. It was given in water as a drink, or as a paste on crackers. On the 9th day after treatment was commenced, and on the 6th day after full doses were used, the reticulocytes reached 12.1%. According to the statistics collected by Bethell and Goldhamer,[3] the average expected maximum reticulocyte percentage following oral administration of

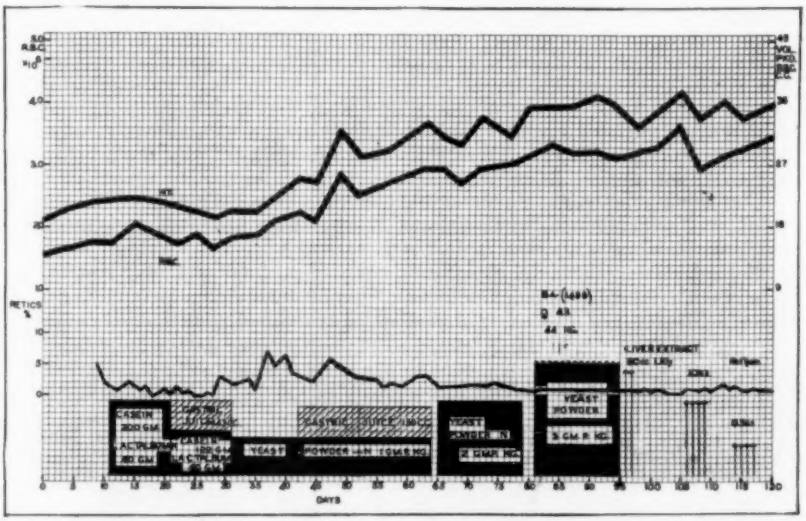

FIG. 3.—Patient B. A., showing submaximal response to a small quantity of brewers' yeast and additional effect of this quantity of yeast after mixture with normal gastric juice.

liver extract from 600 gm. of liver daily in this case was 4.9%. On the 10th day the erythrocyte count had increased from 2,620,000 to 3,190,000 and a level of 4,060,000 was reached 32 days after treatment was started.

Dehydrated brewers' yeast effective in causing well-marked reticulocytosis and red cell formation in doses of 2.2 gm. per kg. No well-defined additional effect produced by mixture with 150 cc. gastric juice. E. R. (No. 1425) (Fig. 2, left), had had recurring attacks of cystitis for 30 years; the blood-vessels were thickened. The catheterized urine contained numerous leukocytes. Urine culture showed a moderate growth of α streptococci.

Ten days after admission, dehydrated brewers' yeast powder (N) was given in doses averaging 2.2 gm. per kg. daily for 10 days. This was given in water as a drink, or as a paste on crackers. On the 5th day following, the reticulocytes had reached a level of 15.8%. The expected maximum increase in reticulocytes[3] was 15.6%.

For the next 11 days, a slightly smaller quantity of yeast (2 gm. per kg.) was given together with 150 cc. of gastric juice. The gastric juice, obtained from normal fasting individuals following the injection of histamine, was neutralized just before mixing it with the yeast, and the whole mixture was promptly fed without incubation, as Castle and Ham recently advised.[5]

A slight secondary rise in the reticulocytes to a maximum of 4.1% on the 6th day followed. The erythrocytes continued to rise and 23 days after yeast therapy was commenced the count had increased from 1,900,000 to 3,470,000. During subsequent treatment with liver extracts parenterally (10 injections of 3 cc. each of liver extract made by ourselves, 1 cc. representing 5 gm. liver; 2 injections of liver extract, Lilly, unconcentrated, 10 cc. each), no further increase in reticulocytes occurred, and the erythrocytes gradually increased to 3,800,000 at the time of discharge.

After acid-washed casein and lactalbumin showed no antianemic potency even when given with gastric juice, yeast in doses of 1 gm. per kg. caused hematopoietic effect. Mixture of this quantity of yeast with gastric juice was followed by a secondary reticulocytosis. B. A. (No. 1428) (Fig. 3): blood pressure 164/90, marked dental caries. Casein and lactalbumin, acid-washed in our own laboratory, were given mixed with water, in amounts averaging 200 gm. of casein and 60 gm. of lactalbumin, daily for 10 days. No significant change in the blood occurred. These were then given in amounts averaging 122 gm. of casein and 35 gm. of lactalbumin, together with 143 cc. of normal gastric juice which had been neutralized just before mixing. On the 8th day, the reticulocytes rose to 3.4% but the erythrocytes did not increase in number.

The same yeast powder (N) which had been given patients C. B. and E. R. was next given in doses of 1 gm. per kg. daily for 11 days. On the 6th day following, the reticulocytes had reached a level of 7% and by the 10th day the erythrocyte count had risen from 1,810,000 to 2,260,000. The expected maximum increase in reticulocytes when extract from 600 gm. liver is given was 17.1%. In the succeeding periods of 10 and 12 days, the same quantity of yeast was given with 150 cc. of normal gastric juice daily, the two periods differing only in that the sources of the gastric juice were different. The gastric secretion was neutralized, mixed and fed in the manner already described.

On the 5th day following the administration of the yeast-gastric juice mixture, the reticulocytes had risen again to 5.8% and on the 10th day the erythrocyte count was 2,510,000. At the end of the 22 days during which this mixture was given, the erythrocyte count was 2,950,000.

During subsequent periods, as shown in Figure 3, yeast was given without gastric juice in amounts equivalent to 2 and 3 gm. per kg. daily. During the last period, probably not all the yeast given was consumed. No further reticulocyte increase occurred and, at the end of the period of yeast therapy, the erythrocyte count was 3,240,000. Liver extracts were than given intramuscularly (10 cc. of an extract made by ourselves daily for 8 doses, then 0.5 cc. Reticulogen (Lilly) daily for 4 doses), but on discharge, 24 days after injections of liver replaced yeast therapy, the erythrocyte count was only 3,420,000.

Administration of beef muscle ineffective; brewers' yeast in doses of 1.5 gm. per kg. caused maximal hematopoietic response; no further improvement on parenteral liver therapy. G. Y. (No. 1559) (Fig. 2, right); moderate arteriosclerosis. Two days after admission the patient was given 200 gm. beef muscle daily for 14 days. No reticulocytosis occurred and the erythrocyte count dropped slightly. The patient was next given dried brewers' yeast (N), 1.5 gm. per kg. daily, in divided doses mixed in water and flavored with chocolate, after meals. On the 10th day following the commencement of this treatment the reticulocytes reached a peak of 27.3% and the red cell count rose quickly, reaching 4,160,000 48 days after treatment was begun. The expected maximal reticulocyte percentage was 26%.

After 3 months of yeast therapy, this treatment was discontinued in order to see if parenteral liver treatment would bring further benefit. For 11 weeks Campolon (Winthrop), 10 cc. was given each week. No further increase in the blood count occurred.

In a patient whose diet had been inadequate, a hematopoietic response followed administration of beef muscle; a second response followed yeast therapy. C. V. (No. 1558) (Fig. 4, left), owing to his false teeth, had taken a diet poor in meat for the past 6 to 8 years, although he had eaten liver about once every 2 weeks. Commencing 3 days after admission, 200 gm. of beef muscle were given daily. On the 9th day following, the reticulocytes had increased to 9.7%. This was substantially less than a maximal response. The rise of the reticulocyte curve was gradual but its fall was precipitous. On the 4th day after the peak had appeared, the reticulocytes were 1.8%.

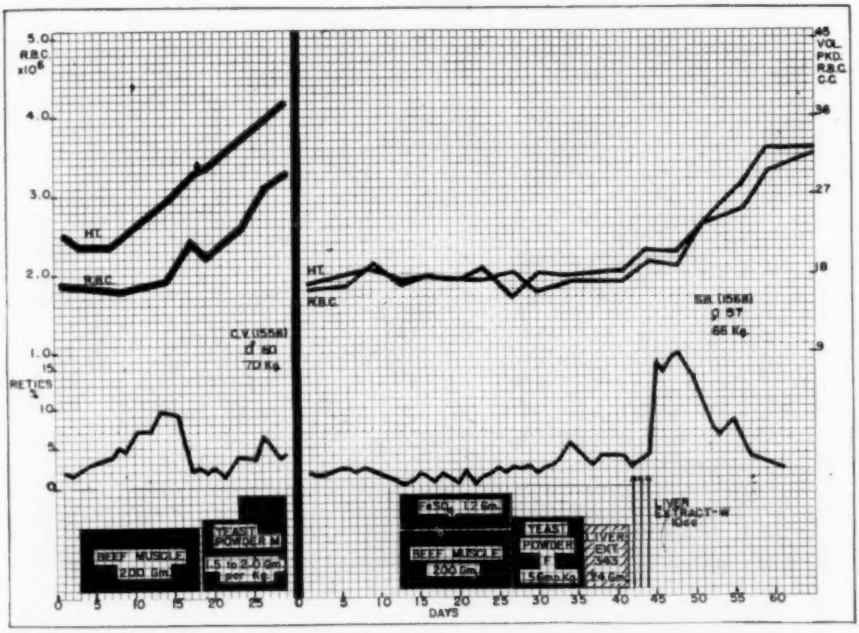

FIG. 4.—At the left, Patient C. V., showing hematopoietic response to "extrinsic factor" (beef muscle) and secondary response to brewers' yeast; at the right, Patient S. B., showing ineffectiveness of oral therapy and maximal response to parenteral liver therapy. There was a slight reticulocyte rise when bakers' yeast was given and no additional effect when large doses of liver extract were given by mouth.

The patient was next given brewers' yeast powder (M), 1.5 gm. per kg. daily, mixed in water and taken after meals. This was continued for 4 days, when the dose was increased to 2 gm. per kg. daily, an amount which was taken for 6 days. On the 7th day following the commencement of yeast therapy, the reticulocytes had risen again to 6.2%. The expected maximum rise under oral liver therapy was 9%.

No response to beef muscle and iron, slight reticulocyte response to bakers' yeast, no additional response to liver extract taken by mouth. Good hematopoietic response to liver parenterally. S. B. (No. 1568) (Fig. 4, right): markedly carious teeth. After a preliminary period of observation of 12 days, beef muscle, 200 gm., was given daily for 2 weeks, as well as ferrous sulphate, 1.2 gm. daily. The reticulocyte and red cell count remained unchanged. A bakers' type yeast (F) was then given for 9 days in amounts corresponding to 1.5 gm. per kg. body weight daily. On the 7th day the reticulocytes had risen to 5.4% but the erythrocyte count increased very little. In a succeeding period of 6 days she was given liver extract (Lilly, 343), 24 gm. daily by mouth. The reticulocytes failed to rise. Liver extract (Compolon,

Winthrop) was then given intramuscularly in 3 doses of 10 cc. each. On the 6th day thereafter the reticulocytes had risen to 16.6% and the red cell count increased promptly.

In a case complicated by chronic bronchitis, sinusitis and emphysema, no response to beef muscle or to yeast extract given parenterally. Reticulocyte responses without increase in erythrocyte count, to a yeast extract, brewers' yeast and liver extract given orally. Good hematopoietic response to liver extract given parenterally. M. K. (No. 1557) (Fig. 5), a former coal miner, coughed frequently and expectorated a white, thick sputum occasionally

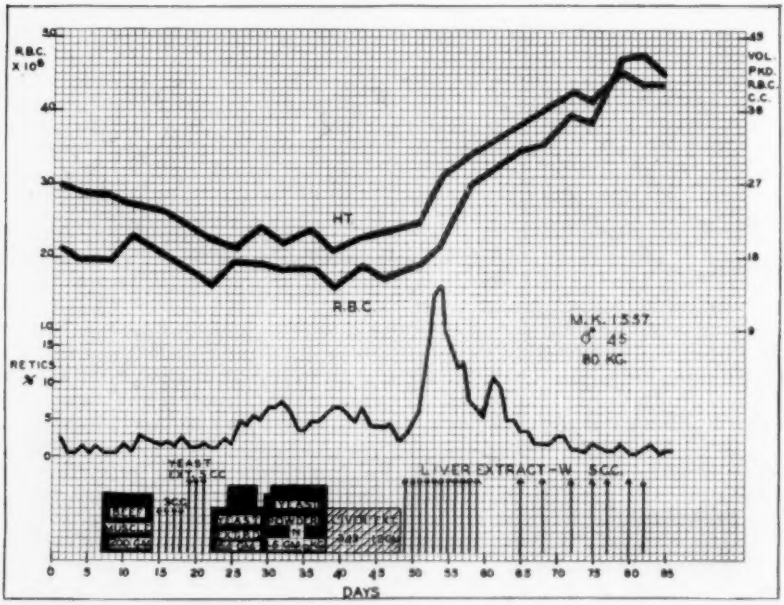

FIG. 5.—Patient M. K. (pernicious anemia complicated by chronic bronchitis and sinusitis), showing ineffectiveness of "extrinsic factor" (beef muscle) and of a yeast extract given parenterally, small reticulocyte responses of equal magnitude to an aqueous extract of brewers' yeast, whole brewers' yeast, and liver extract, all given by mouth, and maximal response to liver extract given parenterally.

streaked with blood. The chest was emphysematous and there were numerous râles at both lung bases extending as high as the scapula on the right side, which persisted after coughing. Roentgen ray of the lungs showed non-tuberculous infiltration of both roots.

After 8 days' observation, 200 gm. beef muscle were fed daily for 7 days. No significant change in reticulocytes occurred. A yeast extract (YL) was next given intramuscularly, 3 cc. for 4 doses and 5 cc. for 3 doses. The blood count continued to drop. An extract of yeast (P.D. 915385) was then given in quantities corresponding to the amount derived from 7.4 gm. yeast per kg. body weight daily for 8 days. On the 7th day the reticulocyte count rose to 6.6%. In a succeeding period of 8 days, whole brewers' yeast (N) was given in amounts corresponding to 1.5 gm. per kg. By the 8th day the reticulocytes had risen again to 6.6% but the erythrocyte count had still not increased.

Liver extract (Lilly, 343) was then given by mouth in 10 daily doses of

12 gm. each. After a slight drop, the reticulocytes reached a maximum of 6.6% on the 4th day of liver therapy. The erythrocyte count, however, remained essentially unchanged. Well-marked hematopoietic response occurred only after liver extract (Campolon, Winthrop) was given parenterally (5 cc. daily). On the 5th day the reticulocytes had increased to 23.4% and the red cell count rose promptly.

Ineffectiveness of beef muscle and of yeast in small doses given orally in a patient who had previously not responded to liver by mouth. Reticulocytosis following yeast extract given parenterally, followed by increase in number of erythrocytes. Slight reticulocytosis without increase in erythrocyte count following administration of liver extract by mouth. Submaximal reticulocytosis with prompt increase in red cell count following parenteral liver therapy.

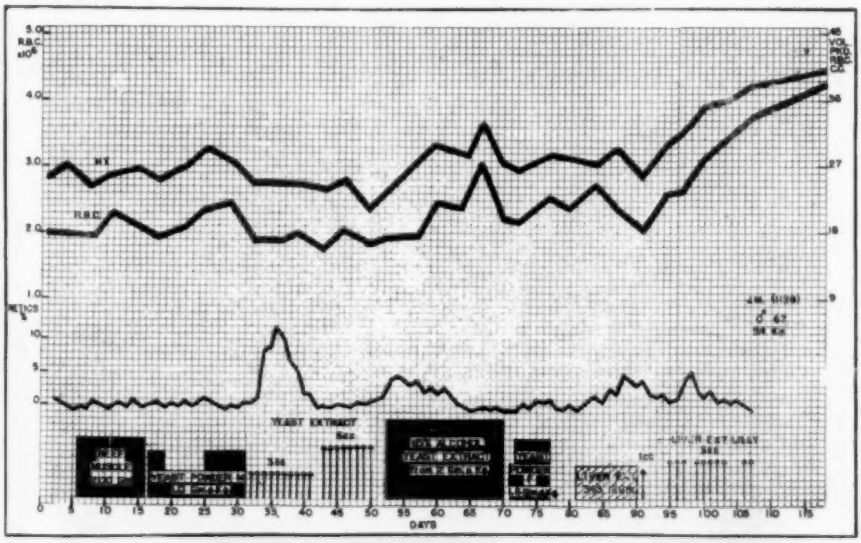

FIG. 6.—Patient J. M., showing reticulocytosis with some increase in the red cell count following parenteral yeast therapy in a patient who failed to respond adequately to yeast or liver extract given by mouth, and who subsequently responded to parenteral liver therapy.

J. M. (No. 1128) (Fig. 6): symptoms of angina pectoris and slight congestive failure, marked arteriosclerosis, blood pressure 150/80. On a previous admission he had failed to respond to "domestic liver extract,"[4] given by mouth, 600 cc. daily for 12 days, but responded to liver extract intramuscularly.

Five days after admission he was given 200 gm. beef muscle daily for 10 days. No change occurred in the blood. Brewers' yeast powder (M) was next given, 1 gm. per kg. daily. This was taken very poorly, however, there being considerable nausea and vomiting. Although the yeast was offered daily for 15 days, it is difficult to state how much was actually retained. Possibly this amounted, on the average, to one-half the quantity given. No reticulocytosis developed, and the erythrocyte count dropped slightly.

An extract of yeast (Y_3), made by a process used in manufacturing liver extract was given intramuscularly, 3 cc. daily for 10 days. Each cc. of this extract was derived from 5 gm. of yeast. On the 5th day following, the reticulocytes had risen to 12.3%. The erythrocyte count, however,

did not change. After a day's pause, the same extract was given in 8 doses of 6 cc. each. On the 3d day after the *last* injection of this extract the reticulocytes had increased again to 5.4% and following this the erythrocyte count rose, for the first time, from a previous level of 1,890,000 to 3,010,000 on the 19th day after the last injection. This increase in reticulocytes and in red corpuscles actually occurred while the patient was receiving a 65% alcohol extract of yeast, given in quantities corresponding to the amount derived from 2 gm. yeast per kg. body weight. The reticulocyte increase appeared on the second day of the alcohol extract period, however, and it would therefore seem that, if this was a specific response at all, it was more probably a response to the parenteral yeast therapy than to the alcohol

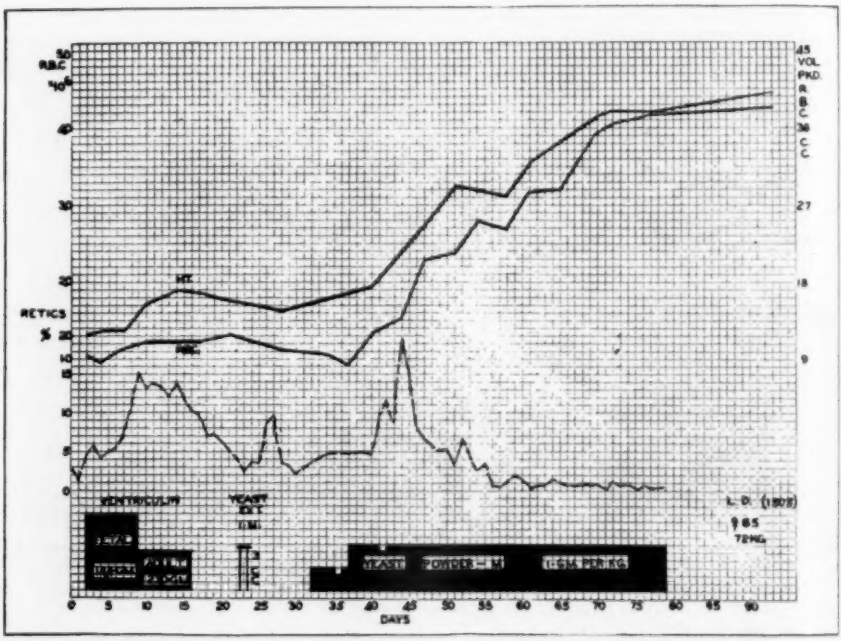

FIG. 7.—Patient L. D., showing reticulocytosis following 2 injections of yeast extract after a submaximal response had occurred to desiccated hogs' stomach Subsequent prompt response to brewers' yeast given by mouth.

extract (Fig. 6). The ineffectiveness of the alcohol extract was indicated by the fact that the red cell count had dropped by the end of the period of administration of this extract.

The patient was next given bakers' yeast powder (F) in amounts equivalent to 1.5 gm. per kg. body weight. Nausea and vomiting developed and this treatment was therefore abandoned after 5 days. The blood did not change. During the next 10 days he received liver extract (Lilly, 343), 12 gm. daily. Reticulocytes increased to 5.3% on the 7th day but the number of red cells failed to increase. Finally, liver extract was given intramuscularly (Reticulogen, 0.5 cc. 1 dose, solution liver extract, Lilly (unconcentrated), 3 cc. daily for 10 doses). The rise in reticulocytes to 6.4% occurring on the 7th day was submaximal,[16] but the red cell count rose to 4,250,000 4 weeks after parenteral liver therapy was started.

After responses to desiccated hogs' stomach, reticulocytosis again occurred following the administration of a small quantity of yeast intramuscularly, and rapid hematopoiesis followed the use of brewers' yeast powder in doses of 1 gm. per kg. This effect occurred in a patient with marked arteriosclerosis and latent syphilis. L. D.* (No. 1505) (Fig. 7): generalized arteriosclerosis and arteriosclerotic heart disease, blood pressure 138/70, pyorrhea alveolaris, blood Wassermann and Kahn tests positive.

This patient was first given ventriculin made from the stomachs of pig fetuses, 14.4 gm. daily for 7 days. On the 7th day following, the reticulocytes had risen to 15.3% and the erythrocyte values had also risen. In the succeeding period of 7 days she was given commercial ventriculin, made from the stomachs of adult pigs, 23 gm. daily. The reticulocytes failed to fall in the customary fashion but, on the 5th day following the first administration of commercial ventriculin the reticulocytes were 14%.

Treatment was discontinued for 5 days and on the 6th an extract of yeast (Y_1) made by a method that is used for making liver extract, was injected intramuscularly, 3 cc., on 2 successive days. Each cc. of this extract was derived from 5 gm. of yeast. The injection caused discomfort and had to be discontinued. Nevertheless, on the 5th day following the first injection the reticulocytes had risen to 9.4%. The erythrocyte count, however, did not rise.

Brewers' yeast powder (M) was next given, in doses of 1 gm. per kg. daily. For several days the amount consumed was uncertain because of nausea and lack of coöperation, but subsequently the yeast was taken regularly. Reticulocytes reached a peak of 19.6%. The erythrocyte values rose quickly and in 35 days the erythrocyte count increased from 920,000 to 4,070,000.

In a case in which a poor response to liver parenterally had occurred on a previous admission, yeast extract parenterally and "wet" yeast by mouth were ineffective, dried brewers' yeasts by mouth caused reticulocyte responses without sustained rise in erythrocyte count, and a submaximal hematopoietic response finally occurred when desiccated hogs' stomach was given. The red cell count of M. Th. (No. 567) on an earlier admission had been as low as 750,000. The anemia on that occasion responded satisfactorily to parenteral liver therapy, but, following a relapse due to discontinuation of a liver diet, the response to liver extracts of known potency given intramuscularly was poor and as the blood count rose the mean corpuscular volume fell below normal. Cessation of liver therapy and administration of iron, however, was followed by another relapse (R.B.C., 2,730,000; M.C.V., 98 c.μ).

Yeast extract (Y_1) was given intramuscularly in 11 daily doses of 3 cc. each, without effect on the blood. Another extract (Y_2) in the same dosage was also ineffective. Whole brewers' yeast (Mw) which had not been desiccated, was given in doses equivalent to 1.5 gm. per kg. daily for 10 days. This caused no reticulocytosis. The same brand of yeast was then given as the dried powder, in doses of 1 gm. per kg. for 10 days. Reticulocytes increased to 4.2% on the 7th day. Another brand of brewers' yeast (N), taken in this dose for 13 days, was associated with a reticulocyte increase to 7.8% on the 12th day and for the first time the erythrocyte count began to rise. This effect did not persist, however, even though a larger quantity (2 gm. per kg.) was taken and ferrous sulphate was given as well. Desiccated hogs' stomach (ventriculin, Parke, Davis Company) was finally given, 30 gm. daily. Reticulocytes increased to 14.2% on the 8th day (expected percentage 22.2) and the erythrocyte count rose slowly from 1,800,000 to 3,490,000 7 weeks later.

* I am indebted to Dr. Robert Kirk and Dr. C. H. Kosmaler for permission to use this case.

In a hypertensive arteriosclerotic with urinary tract infection, an extract of yeast, whole brewers' yeast and liver extract given orally caused various degrees of reticulocytosis without increase in the red cell count. Submaximal hematopoietic response followed parenteral liver therapy. M. T. (No. 258) (Fig. 8) complained of precordial pain and was found to have arteriosclerosis, hypertension (blood pressure 214/110), cardiac enlargement, dental caries, hydronephrosis and chronic urinary tract infection.

After a week's preliminary observation, an extract of yeast (P.D. 913807) was given in quantities corresponding to the amount derived from 4 gm. of yeast per kg. body weight, for 10 days. On the 10th day a slight rise in the reticulocytes to 3.8% occurred. In the succeeding period of 10 days,

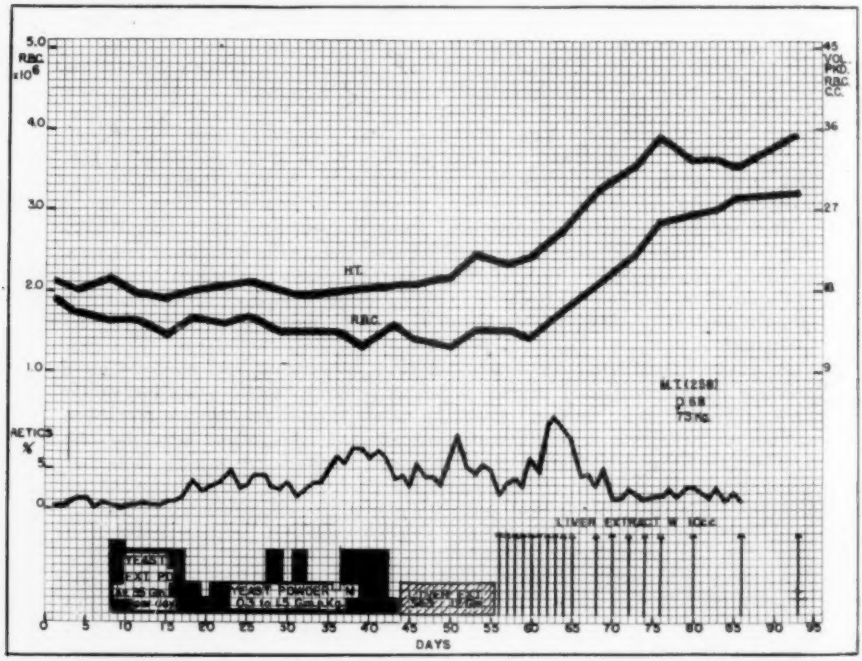

FIG. 8.—Patient M. T., showing failure of red cell count to rise in spite of reticulocytosis following oral therapy with yeast extract, whole brewers' yeast and liver extract: submaximal response to parenteral liver therapy.

whole brewers' yeast powder (M) in amounts corresponding to 0.7 gm. per kg. was given. Reticulocytes increased to 5% on the 5th day. During the next 16 days the same yeast was taken somewhat irregularly in amounts averaging about 1.1 gm. per kg. With this increased dosage the reticulocytes rose again, to a maximum of 7.8%. During all this time, however, no significant increase in the red cell count occurred.

In the succeeding period of 10 days, liver extract (Lilly 343) was given by mouth in doses of 12 gm. daily. On the 5th day, the reticulocytes reached a peak of 9.2% but the erythrocyte count still failed to rise. Finally, on intramuscular liver therapy (Campolon, Winthrop), 5 cc. daily, reticulocytes increased to 11.4% on the 7th day and for the first time the red cell count began to rise. The rise was slow, however, in spite of the fact that treatment of the urinary tract infection was instituted at this time.

No response to yeast extract or to bakers' yeast; slight response to brewers' yeast; more marked response to liver extract given by mouth. No response to

yeast extract given parenterally; good response to liver extract given parenterally. L. B. (No. 1609) (Fig. 9), after 7 days' observation during which time the reticulocytes rose as high as 10% although the red cell count did not increase, an extract of yeast (P.D. 913807) was given for 10 days in quantities corresponding to the amount derived from 3 gm. of yeast per kg. body weight. During this time the reticulocyte count decreased from the spontaneous rise of 10% to 2.4% on the 5th day after treatment with yeast extract was started, and only a slight upward turn to 5.1% occurred on the 8th day after the yeast extract was first given.

In the next period, a bakers' yeast powder (F) was given for 9 days in amounts equivalent to 1.5 gm. per kg. daily. No hematopoietic response

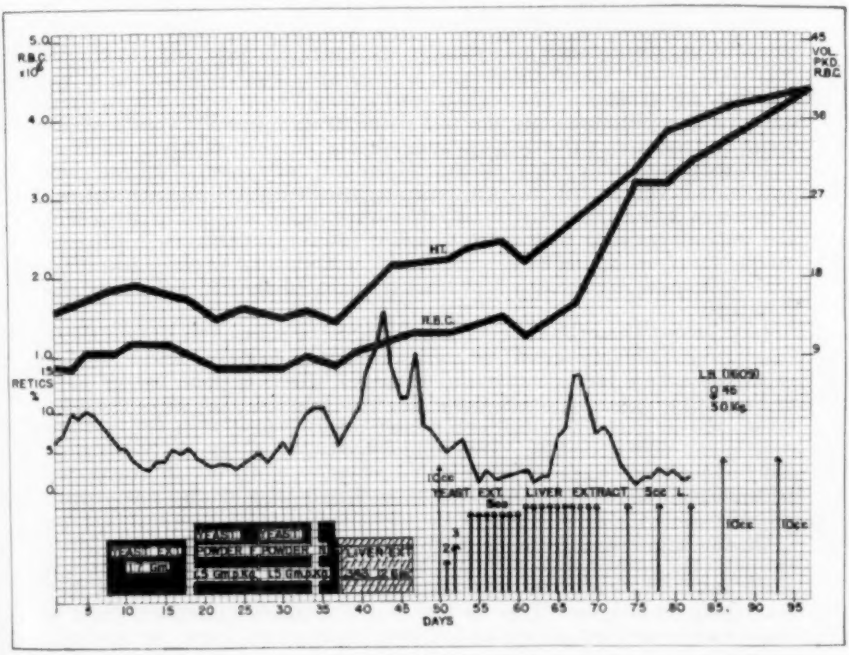

FIG. 9.—Patient L. B., showing ineffectiveness of a bakers' yeast, moderate hematopoietic effect of brewers' yeast and better response to liver extract, all given by mouth.

occurred. A brewers' yeast powder (N) was then given in similar amounts for 8 days. On the 6th day the reticulocytes had increased to 10.4%. Owing to the severity of the patient's anemia, yeast therapy was not continued, but instead liver extract (Lilly, 343), 12 gm. daily, was given orally for 10 days. On the 7th day of this period of treatment, the reticulocytes had risen to 21.8% and the erythrocyte count had begun to increase. The expected reticulocyte percentage[3] was 35%.

After a pause of 3 days, an extract of yeast (YL) was given intramuscularly in doses averaging 5 cc. daily for 10 days. No increase in reticulocytes occurred, nor did the erythrocyte count rise. Following this, solution liver extract (Lilly, unconcentrated), 5 cc. daily, was given in 10 doses. Reticulocytes increased to 14.6% on the 7th day following and the erythrocyte count rose to 3,420,000 3 weeks after commencement of parenteral liver therapy.

No response to bakers' yeast, moderate response to brewers' yeast, secondary response to liver extract given parenterally. L. E. S.* (No. 1635) (Fig. 1, right), moderate arteriosclerosis, leukoderma. After a preliminary period of observation, a bakers' type of yeast (F) was given, in amounts equivalent to 1.5 gm. per kg. body weight daily for 10 days. The reticulocyte percentage failed to change and the red cell count dropped. For the next 20 days he was given brewers' yeast (M) in the same amounts. On the 9th day the reticulocytes had increased to 13.4% and at the end of this period a moderate increase in the red cell count had occurred. Liver extract (Lederle) was next given intramuscularly, 2 cc. daily for 3 days and 1 cc. daily for 5 doses thereafter. Reticulocytes increased to 13.3% on the 6th day and the erythrocyte count rose promptly.

Little change in blood after bakers' yeast or liver extract by mouth. Improvement following parenteral liver therapy. J. Mc. (No. 649), red blood cells 3,410,000, after 7 days' observation was given bakers' yeast, 1.5 gm. per kg. daily for 21 days. The highest level attained by the reticulocytes was 4.6% on the 18th day. By the end of the 21-day period the erythrocyte count had not risen although some symptomatic improvement had occurred.

Liver extract (Lilly, 343) was next given in 9 daily doses of 12 gm. each by mouth. On the 9th day the reticulocytes were 6.4% and the red cell count was 3,220,000. Further detailed observation was not possible but the patient received liver extract (Lilly) intramuscularly, in 2 doses of 20 and 10 cc. each, and 10 cc. each week for the next 4 weeks. Six weeks after intramuscular therapy had been commenced the red cell count was 4,100,000.

In a patient known to respond only slowly to large amounts of stomach or liver extracts given by mouth, no response occurred following administration of a yeast extract given parenterally, an alcohol extract of yeast, bakers' yeast or liver extract given by mouth, but a slow rise occurred when whole liver was taken. E. G. (No. 1396) had been treated a year before, when the erythrocyte count was 2,650,000. The administration of 40 gm. of ventriculin daily at that time was associated with a reticulocyte rise of 3.2% (expected percentage 9) and the erythrocyte count rose only when double this amount was given.

On this admission, when the erythrocyte count was 2,180,000, a yeast extract (Y_2), prepared somewhat differently from that given to patients L. D. and J. M., was given intramuscularly, 3 cc. daily for 2 doses and then 6 cc. daily for 8 doses. This, as well as a 65% alcohol extract of yeast in doses corresponding to an amount of yeast representing 2 gm. per kg. body weight daily for 4 days and 5 gm. per kg. for 3 days, caused no reticulocytosis and the red cell count gradually fell. The injection of liver extract (J. H. H.) in 5 doses of 1.5 cc. and 5 doses of 3 cc. was followed by an increase of reticulocytes to 15.2% on the 8th day (expected percentage 23) and a rise in the erythrocyte count.

The patient returned 4 months later, again somewhat anemic but with no complaints. He had taken no treatment for almost 2 months and then took bakers' yeast somewhat irregularly. (R.B.C., 2,890,000; M.C.V., 108 c.μ.) He was given bakers' yeast (F), 1.5 gm. per kg. per day for 10 days. On the 6th day reticulocytes were 4.4% but the red cell count failed to increase. A similar quantity of brewers' yeast (M) was then given for 10 days. No reticulocyte increase occurred and the blood was unchanged. The dose of brewers' yeast was doubled (3 gm. per kg.), but even this large amount failed to produce a hematopoietic response. Liver extract (Lilly, 343) was then given, 16 gm. daily for 8 days, 24 gm. daily

* I am indebted to Dr. W. K. Waller, University Hospital, for his assistance in this case.

for 9 days. The last dose is the amount derived from 600 gm. liver. Even this large quantity of liver extract was without significant effect. Only when whole liver, ½ pound daily, was consumed did the erythrocyte count begin to rise.

Comment. *Maintenance Treatment.* A number of patients whose blood was already normal, or nearly so, were given yeast in place of the oral or parenteral liver therapy they had been taking. These patients have been studied in the out-patient department and have been allowed to take their usual diets, without liver. Ten have received this treatment for 4 to 10 months (Table 2), while several others have been given yeast for shorter periods of time. Two of the 10 (E. R. and M. K.) were also given yeast while in relapse and their histories are recorded above.

TABLE 2.—CASES ON MAINTENANCE TREATMENT WITH YEAST.

Patient.	Age.	Sex.	Weight, kg.	Average dose of yeast, gm. per kg.	Duration of treatment, months.	Volume of packed red cells, cc. per 100 cc. blood.	
						At start.	At present.
L. E.	65	F	68	0.7	10	39.0	39.3
N. H.	39	F	70	0.3	9	40.0	42.0
E. R.	69	F	75	0.3	10	40.3	39.8
G. S.	48	F	59	0.5	8	40.2	40.0
M. A.	63	F	55	0.3	7	40.8	40.0
E. W.	65	F	64	0.7	6	40.0	43.4
J. S.	54	M	73	0.8	6	47.0	42.0
C. M.	61	F	56	0.4	4	37.0	39.2
M. K.	45	M	77	0.5 "N"	2	42.2	43.8
				0.3 "F"	2	43.8	31.8
J. G.	61	M	82	0.8	4	44.0	44.0

The quantity of yeast consumed has ranged from 0.3 to 0.8 gm. per kg. body weight daily. The yeast used was a brewers' type (N or M), except in several cases for a period of 2 months when a bakers' yeast (F) was given. These patients were subsequently given brewers' yeast again.

In all but 1 of the cases, the blood has remained essentially unchanged (Table 2). The single instance of relapse occurred in a patient (M. K.) who had chronic bronchitis and was subsequently shown to respond poorly to oral therapy (see above, Fig. 5). When he was first seen the erythrocyte count was 3,710,000, the volume of packed red cells 42.2 cc. He took brewers' yeast (N), 0.5 gm. per kg. per day, for 2 months. There was symptomatic improvement and the red cell count increased to 4,400,000, the volume of packed red corpuscles to 43.8 cc. For the next 2 months he took bakers' yeast (F) in smaller doses (0.3 gm. per kg.). The erythrocyte count dropped to 3,000,000, the volume of packed red cells to 31.8 cc.

Effect on Symptoms. In the patients treated with yeast while in relapse, when a hematopoietic response was obtained, symptomatic improvement like that associated with liver therapy occurred as

well. It was often difficult to induce the patients in relapse to take large amounts of yeast but after a few days, sometimes even before the reticulocytes had commenced to increase, appetite improved and even 120 to 150 gm. of yeast were readily consumed daily. Some patients have expressed preference for yeast as compared with liver, while others complained of distention or even nausea. In a few cases, nausea, vomiting and diarrhea developed, even when small quantities of yeast were being taken. It is impossible to say whether these symptoms were always due to the yeast, because some of these patients had been able to take yeast without trouble before, and in some instances they have taken it since these symptoms developed. One patient (E. R.) who complained of distention took liver for a few days instead and, finding the distention even more severe, resumed yeast which she has taken ever since.

Sore tongue developed in 2 cases (G. S. and B. A.) while yeast was being taken. In G. S. (Table 2), with continuation of treatment, the pain disappeared although the tongue remained beefy red. Sore tongue has always been this patient's chief complaint and this symptom had previously recurred while she was receiving oral liver therapy. It had been effectively relieved only by parenteral liver therapy. Parenteral liver therapy was also necessary for the relief of patient B. A.'s glossitis. The main complaint of patient C. M. (Table 2) was sore tongue. Temporary relief followed yeast therapy. When glossitis recurred, liver extract (Lilly, 343), 8 gm. daily, was given. After several weeks some symptomatic improvement occurred, even though the blood remained the same throughout the periods of yeast and liver therapy. None of the remaining patients were troubled by glossitis.

The patients described in this report had minimal neurologic symptoms and signs. In such cases it is difficult to evaluate the effect of therapy on the nervous system until treatment has been continued for a long time. Consequently comment here on this aspect of the treatment of pernicious anemia by means of yeast is omitted.

Discussion. As has been observed frequently in connection with the response of different individuals to liver or liver extracts, especially when orally administered,[19] there was considerable variation in the response of these patients to yeast. In 3 cases (C. B., E. R. and G. Y.) brewers' yeast in amounts of 1.5 to 2.2 gm. per kg. body weight daily, produced reticulocyte responses which were greater than the average expected values[3] following the daily use of liver extract derived from 600 gm. fresh liver, and a rapid increase in the erythrocyte count followed. In 1 case (L. D.) brewers' yeast, in doses of 1 gm. per kg. daily caused a well-marked reticulocytosis even after a good reticulocyte response to suboptimal amounts of desiccated hogs' stomach had occurred, and very rapid regeneration

of red cells followed. The same yeast caused a satisfactory hemopoietic response in patient C. V. The submaximal reticulocytoses in these last 2 cases were obviously due to the fact that a substantial reticulocytosis to other substances had already occurred.

Submaximal responses occurred in patients B. A. and L. E. S. to brewers' yeast given in quantities of 1 and 1.5 gm. per kg., respectively. In 1 of these (B. A.) subsequent parenteral liver therapy failed to produce further response than was obtained from yeast, and in the other (L. E. S.) the response to liver was submaximal. In 3 cases (M. K., M. T. and E. G.) brewers' yeast caused slight or no reticulocytosis and no significant increase in the red cell count, but liver extract in amounts derived from 300 to 600 gm. of liver, given by mouth, also failed to produce an increase in the red cell count although in 2 of these patients (M. K. and M. T.) reticulocytosis of equal degree to that following oral yeast therapy occurred. In 1 of these patients (M. T.) even parenteral liver therapy did not produce an optimal effect. Only in 1 patient (L. B.) was liver extract given orally followed by a definitely better response than that which followed administration of brewers' yeast given in doses of 1 or more gm. per kg. In another patient (M. Th.), whose response to oral therapy was poor, desiccated hogs' stomach was somewhat more effective than brewers' yeast.

As already mentioned, 9 patients receiving brewers' yeast as maintenance therapy have remained well to date, 4 to 10 months after commencement of this form of treatment.

Bakers' yeast (F) was given to 6 patients. In none did a satisfactory response occur. In 2 patients (L. B. and L. E. S.), brewers' yeast given subsequently in the same amounts caused a definite hematopoietic effect although in neither case was this as marked as has been observed in other cases. In 4 patients (S. B., J. M., J. Mc. and E. G.) the absence of a significant response to bakers' yeast was followed by a similar failure of oral liver therapy, and parenteral treatment with liver was necessary. In addition to these cases, relapse occurred in 1 patient (M. K.) while he was taking bakers' yeast as maintenance therapy.

It should be emphasized that the patients who were the subjects of the experiments reported here presented the clinical picture which is generally accepted as that of classical pernicious anemia. The opinion has been expressed that macrocytic anemia due to deficiency of extrinsic factor, rather than of intrinsic factor as occurs in pernicious anemia, may be readily confused with the latter, and Groen and Snapper[14] recently described several such cases. Unlike Groen's cases, however, our patients not only had achlorhydria but there was the total lack of gastric secretion and low combined acidity characteristic of pernicious anemia, as well as persistence of achylia after the anemia had been relieved; many of our patients had suffered

one or more relapses following discontinuation of liver therapy, whereas Groen's patients remained well for a long time on a mixed diet not deliberately supplemented with liver; and finally, with one exception, there was no history of defective diet. This last argument is not stressed, however, because it is difficult to obtain accurate accounts of a patient's diet.

In view of the length of the periods of observation and the number of cases studied, the hematopoietic effects associated with the administration of yeast do not appear to be fortuitous. It seems fair to say that dehydrated brewers' yeast when given orally, may cause a hematopoietic response in cases of pernicious anemia which is as great as that produced by oral administration of liver extract derived from a quantity of liver 2 to 8 times the weight of the brewers' yeast used. Even when it is recalled that dehydrated brewers' yeast contains only 9% moisture, while that of fresh liver is much greater, the antianemic effectiveness of dehydrated brewers' yeast compares favorably with that of liver.

In his well-known experiments,[6] Castle showed that when the gastric juice of normal persons is mixed with beef muscle, the "intrinsic factor" normally secreted by the stomach interacts with a dietary or "extrinsic" factor to form an "antianemic principle" which is effective in causing a hematopoietic response in cases of pernicious anemia in relapse.

In view of the fact that yeast has been regarded as a good source of extrinsic factor, it is important to know whether the action of yeast in these cases was due to the fact that enough intrinsic factor was secreted by the stomachs of these patients to convert the yeast into antianemic principle. This question is all the more important since it has been demonstrated[11] that the intrinsic factor deficiency in cases of pernicious anemia may not be absolute. Two groups of experiments were carried out in an attempt to answer this question.

Five patients were fed beef muscle, 200 gm. daily for periods of 7 to 15 days. In 4 no change whatever occurred in the blood. Three of these (S. B., M. K. and J. M.) responded poorly to the subsequent oral administration of yeast or liver extract, but 1 (G. Y.) responded promptly and rapidly to brewers' yeast after the blood had not changed under a 14-day régime of beef muscle. The fifth patient (C. V.) is also of great interest because the administration of meat was followed by a reticulocytosis which, though not great, was quite definite and was followed by some increase in the erythrocyte count. This patient, as has already been mentioned, was the only one from whom a history of inadequate diet had been obtained. The reticulocytosis produced by the beef muscle was followed by a second reticulocyte response when brewers' yeast was administered and a more rapid regeneration of red cells, indicating the greater potency of the yeast as compared with the beef muscle.

It should be pointed out that in the comparisons between the

antianemic effectiveness of beef muscle and yeast, the differences in the quantities of protein given were relatively small, and could not account for the differences in the effects produced. On the basis of its nitrogen content, 200 gm. of beef muscle, according to our determinations, contains 39.7 gm. of protein. The quantity of "protein" (N × 6.25) administered in yeast to patients first given this amount of beef muscle ranged from 38.9 to 70 gm. daily. In the case in which the most striking difference between the effectiveness of beef muscle and yeast was noted (G. Y.), the quantity of protein given as beef muscle was 39.7 gm., that given as yeast was 43.5 gm. Furthermore, it should be noted that the quantity of protein in bakers' and in brewers' yeast is the same. Yet a well-marked difference in hematopoietic effect between these two types of yeast has been observed.

In 2 patients yeast was given, at first alone and then after mixture with normal gastric juice. According to Castle's hypothesis, if yeast acts as a source of extrinsic factor, no effect should follow its administration alone but a hematopoietic response should occur when it is given together with normal gastric juice. In the first patient (E. R.), a large quantity of brewers' yeast was given daily for 10 days. A well-marked reticulocyte response occurred. When a similar quantity of yeast was given together with gastric juice from normal persons, no secondary response appeared, indicating that the first effect had been maximal. In the second patient (B. A.), a smaller quantity of yeast was given. A moderate increase in reticulocytes followed. When the same quantity of yeast was given together with gastric juice, a secondary response was observed. This is exactly similar to the effect of mixing gastric juice from normal persons with liver or liver extract.[20]

While these experiments do not exclude the possibility that yeast contains extrinsic factor in so high a concentration that even a minute amount of intrinsic factor can convert it into effective antianemic substance, it seems at least equally plausible that the antianemic factor in yeast differs from that in beef muscle not only quantitatively, but also qualitatively. Yeast has been shown in these studies to resemble in antianemic effect the factor or factors in liver and in desiccated hogs' stomach which are effective when given by mouth.

It has not been proved that the yeast factor is the same as the liver substance which is effective when given parenterally. In 2 patients (L. D. and J. M.) reticulocytosis followed the injection of yeast extract; but, since no well-marked increase in the number of red corpuscles followed, this effect may have been non-specific.

At this time one is not justified in drawing conclusions regarding the nature of the antianemic substance in yeast. It should be pointed out that our understanding of the physiologic disturbance in pernicious anemia is as yet very inadequate and that, although

reference is often made to "extrinsic factor," "intrinsic factor" and "antianemic principle," as if their chemical nature and mode of interaction has already been made quite clear, our knowledge of them is very imperfect. Only recently, Castle and his coworkers[7] have brought evidence that an "intermediate substance" is formed by the interaction of the dietary and gastric factors.

Studies are now being carried out which seek to define some of the properties of the yeast factor. Neither the aqueous nor the alcohol extracts which have been prepared so far, have demonstrated a high degree of potency, although it should be noted that both of the patients to whom the alcohol extract was given (J. M. and E. G.) were shown later to be unsatisfactory for oral tests, and the choice of cases for testing the aqueous extracts (L. B., M. T. and M. K.) was not much better. Of greater interest are the comparisons of the antianemic effectiveness of brewers' and bakers' yeast. Although the data do not prove that antianemic substance is totally lacking in bakers' yeast, they demonstrate that "brewers'" yeast is at least more potent in this respect than "bakers'" yeast. This statement applies, of course, only to the dehydrated yeasts used in these studies but the observation is of considerable interest in view of the fact that there are differences in the manner in which the brewers' and bakers' yeasts used were grown. There is no reason to believe from our present data that the species of yeast is important.

There is no positive evidence at the present time that the yeast factor is one of the recognized water-soluble vitamins. Much of the work undertaken in the studies of yeast recorded in the literature was carried out with the object of discovering what relationship exists between the antianemic principle, or Castle's extrinsic factor, and the "B" vitamins. For this purpose studies have also been made of sources of these vitamins other than yeast, such as wheat embryo,[24] egg-white, rice polishings,[18] riboflavin,[2] and nicotinic acid.[15] None of these has been successful in demonstrating a relationship between one of the "B" vitamins and antianemic substance.

In conclusion, it should be emphasized that these observations are recorded because of the bearing they may have on an understanding of the disease pernicious anemia, rather than with the purpose of proposing a new form of treatment. Although some patients may prefer yeast to liver, the development of liver extracts for parenteral as well as oral use is such that, in general, this method of treatment will probably be desired. Knowledge of the distribution of antianemic substances and their precursors is of importance, however. Moreover, in view of Castle's hypothesis, it is of interest to know whether "antianemic principle" can be produced by a plant without the interaction of substances of animal origin. Furthermore, it may be that a study of yeast may lead to information regarding the antianemic principle and its precursors which it has not been

possible to gain so far by a study of liver. It is along these lines that present investigations are being directed.

Summary. 1. The results of the administration of dehydrated brewers' and bakers' yeast, as well as extracts of these substances, to 15 cases of pernicious anemia in relapse and 8 additional cases with little anemia, are described.

2. Maximal hematopoietic responses occurred in 5 patients given dehydrated brewers' yeast in amounts of 1 to 2 gm. per kg. body weight daily.

3. Submaximal effects occurred in 2 other patients who subsequently were found to respond inadequately to liver. Little response was noted in 3 patients who likewise failed to respond to oral liver therapy. Only in 1 case was liver extract, given by mouth, more effective than brewers' yeast, and in 1 resistant case desiccated hogs' stomach was somewhat more effective than brewers' yeast.

4. Nine patients receiving 0.3 to 0.8 gm. yeast per kg. daily as maintenance therapy, have remained well to date, 4 to 10 months following commencement of this form of treatment.

5. Brewers' yeast induced hematopoiesis without preliminary mixture with gastric juice from normal persons. The effects of the administration of yeast together with normal gastric secretion in 2 cases were similar to those observed when liver or liver extract is given in this way.

6. Four patients given 200 gm. beef muscle daily failed to respond to such treatment; while in 1, in whom a hematopoietic effect did occur, a secondary response to yeast appeared.

7. The difference between the antianemic effect of beef muscle and of brewers' yeast cannot be explained on the basis of differences in the quantity of protein administered.

8. A bakers' type of yeast failed to cause well-marked hematopoietic effects in 6 patients, 4 of whom subsequently did not respond even to oral liver therapy but 2 of whom responded to brewers' yeast.

9. Reticulocytosis occurred in 2 patients given yeast extracts parenterally but a significant increase in the number of red corpuscles did not follow.

10. A significant hematopoietic effect has not been produced by the oral administration of extracts of yeast which have been prepared so far.

11. No conclusion is reached regarding the nature of the hematopoietic substance in yeast, but the differences between the effects of brewers' yeast and "extrinsic factor" as represented by beef muscle, and the similarity of these effects to those produced by liver or liver extracts given orally, are pointed out.

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VITAMIN C DEFICIENCY—CLINICAL AND THERAPEUTIC PROBLEMS.

With a Case Study of Six Patients in One Family.

By Teresa McGovern, B.S., M.D., M.S. in P.H.,
Junior Assistant Physician, New York Post-Graduate Hospital,

Catherine F. Gannon, A.B., M.A.,
Instructor in Clinical Pathology, New York Post-Graduate Medical School,

and

Irving Sherwood Wright, A.B., M.D.,
Associate Clinical Professor of Medicine, New York Post-Graduate Medical School, New York City.

(From the Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.)

Scurvy and allied conditions have been covered exhaustively in the literature of the past 5 years, over 1000 articles dealing with vitamin C having appeared in 1935 alone. It seems appalling, therefore, that this disease should be as prevalent as it is today. The fact that it is actually being precipitated by prescribed courses of therapy indicates that many physicians are failing to recognize the problem because of a belief that scurvy was a scourge in the past, but today is to be associated only with extreme poverty and malnutrition. On the contrary, it is very commonly found, even among the better economic groups, if the physician is acute to the possibility.

It appears worthwhile to review briefly the mechanisms by which hypovitaminosis C may be produced, the common signs and symptoms, the disease syndromes under which it may masquerade, and the criteria for diagnosis, before presenting the report of a mother and 5 adult children exhibiting varying forms and degrees of vitamin C deficiency as a result of familial distaste for its principal food sources. Although well able to afford a balanced diet, they almost never took citrus fruits, tomato juice, or cabbage. The most severe case, that of the mother, has been followed for 21 months, determinations of urinary vitamin C having been made daily for 4 months and weekly thereafter, as well as regular observations of the clinical course of the scorbutic condition by means of the capillary fragility test.[21]

Mechanisms by Which Hypovitaminosis C May be Produced. *A.* Increased demand for vitamin C, as in infections.[1,11] *B.* Destruction of vitamin C, suggested by inability of some individuals to utilize oral doses. *C.* Deficient absorption due to altered chemistry of the gastro-intestinal tract or bacteria.[14,17] *D.* Increased excretion of vitamin C, as is said to occur with indiscriminate use of salicylates.[2] *E.* Idiosyncrasy and, or, hypersensitivity for citrus fruits and other foods rich in vitamin C. *F.* Restriction of vitamin C-containing foods (Sippy diet, colitis diet, faddist diet, poor economic condition.)[21]

Common Signs and Symptoms of Scurvy.[8,18] *A.* Bluish, swollen, spongy gums which bleed easily, or loose teeth. (Gums are usually healthy if teeth have been removed. Dental caries are considered by some workers to be caused in certain instances by vitamin C deficiency.) *B.* Dry scaly skin. *C.* Perifollicular hemorrhages. Hemorrhages under the toe nails. *D.* Tendency to hemorrhage (either petechial or ecchymoses into skin and, or, subcutaneous tissue). *E.* Brawny, tender swellings or indurations in calves, thighs, abdominal wall, popliteal space, and over the tibia. *F.* Weakness, pain in limbs and joints especially after exercise. *G.* Palpitation and breathlessness. *H.* Anemia not amenable to liver or iron therapy. Microcytic, macrocytic, or normocytic in type. Responds to vitamin C with reticulocytosis and recovery. *I.* Constipation or diarrhea with offensive and bloody evacuations. *J.* Hematuria. *K.* Night blindness, while usually associated with vitamin A deficiency, may also be a symptom of vitamin C deficiency. *L.* Loss of weight. Anorexia. *M.* Slight edema. *N.* Fever.

Disease Syndromes Under Which Scurvy May Masquerade. *A.* Rheumatism and allied diseases. *B.* Erythema nodosum. *C.* Lupus erythematosus. *D.* Varicose veins with varicose eczema. *E.* Hemorrhagic nephritis. *F.* Purpura hemorrhagica, thrombocytopenia and other purpuras. *G.* Hemophilia. *H.* Gingivitis. *I.* Neuritis. *J.* Colitis or gastro-intestinal malignancy, especially when hemorrhage is a prominent feature. *K.* Unexplained secon-

dary anemias. *L.* Other peripheral vascular diseases. *M.* Optic hemorrhage. *N.* Osteomyelitis.

Diagnostic Criteria. *A.* Increased capillary fragility[4,8,9,21] when the following diseases and conditions have been ruled out: lues, tuberculosis, kidney diseases, acute infectious diseases, the blood dyscrasias, menstruation, arsphenamine poisoning and gastric achylia. *B.* Under vitamin C therapy alone a return of the fragility to normal with clinical improvement.*[21] *C.* A history of deficient vitamin C intake, or the consumption of large amounts of salicylates.[2] *D.* One or more signs or symptoms listed earlier.[18] *E.* When judiciously evaluated, the chemical tests for cevitamic acid content of body fluids,[5,7] including the saturation determination by the test dose method.[22] As previously pointed out, these tests indicate only the state of saturation of the tissues but not *per se* the disease scurvy.

Case Reports. CASE 1.—The mother, aged 64, in good financial circumstances, was first seen August 21, 1936. The chief complaint was pain in calves after walking one-half block, 8 months' duration. Past history: 8 months previously, the patient developed intermittent claudication in calves after walking half a block necessitating resting for 2 or 3 minutes before walking could be resumed. About 8 weeks before the first visit, she developed pain in both tibiæ, which medication did not relieve; the pain was present whether at rest or exercising. Two weeks before the first visit, discrete red, raised spots appeared along the inner side of left leg, followed in 1 or 2 days by pitting edema of both legs. The reddened areas increased rapidly in size and coalesced. She stated that she thought her "legs would burst."

She has had symptomless hypertension of 10 years' duration (200+ systolic pressure). Seven years ago, she developed a syndrome diagnosed as arthritis, which was preceded by a condition in her legs similar to the present one; however, at that time, several of the reddened raised areas ruptured, requiring many months to heal, with deep scar formation. She states her legs have never been normal since that time. She recalls a return of her so-called arthritis each spring with tibial pain and edema of legs with the symptoms less severe during the summer. The present attack has persisted since early spring and is by far the most severe.

Systems all negative. Seven pregnancies, 5 living children. Family history—negative.

Physical Examination. Well developed, well nourished, white female, obviously in great pain. Eyes: negative; grounds showed sclerosis of vessels. Nose and ears: negative. Mouth: mucous membranes and gums normal; upper and lower dental plates. Chest: heart enlarged to left, rate 88, rhythm regular, loud systolic aortic murmur; blood pressure 184/78; lungs, clear throughout. Abdomen: negative. Extremities: Heberden's nodes of terminal phalanges; oscillometric readings from popliteal arteries distally were zero bilaterally; extending from the internal malleolus to just below the knee, the skin and subcutaneous tissues were hard and indurated; a fluctuating mass was palpable over the left tibia. There were many raised irregularly-shaped tender red areas over the rest of the leg. The right leg was entirely free of these spots. However, both legs showed many perifollicular hemorrhages. A marked decrease in temperature of both legs from

* Method used in these studies was that described by Wright and Lilienfeld.[21] Normal—up to 10 petechial spots; borderline zone, 10 to 20; pathologic, above 20.

the middle of the legs down to the toes was noted, more pronounced in the left. Both legs had 2+ edema.

Capillary Fragility. One hundred petechial hemorrhages in 5 minutes (the arm became so hemorrhagic that the test was terminated at one-third the usual time. Technique used was that described by Wright and Lilienfeld).[21]

Laboratory Results. Urine, negative; 2-hour renal function test (Mosenthal), normal. Wassermann, negative.

Blood chemistry:

Non-protein N	45 mg. %	Chlorides	460 mg. %
Urea N	14 mg. %	CO_2 C.P.	52.8 cc. %
Uric acid	3.2 mg. %	Serum proteins (total)	5.4%
Sugar	85 mg. %	Albumin	3.6%
Cholesterol	150 mg. %	Globulin	1.8%

Diagnosis. 1. Scurvy. 2. Essential hypertension, enlarged heart. 3. Occlusive vascular disease of vessels of legs from popliteal artery distally. Arteriosclerosis. 4. Chronic rheumatoid arthritis.

Present Illness. For 7 years this patient had been under treatment for rheumatoid arthritis and had at intervals taken large amounts of salicylates. At the same time, she was on restricted vitamin C intake because of an idiosyncrasy for citrus fruits and the ordinary vitamin C-containing foods. Coincidentally, her protein intake had been greatly curtailed because of her hypertension.

When the patient was first seen, August 21, 1936, she had been suffering from what had been diagnosed as arthritis since early Spring, and her condition was becoming progressively worse, even though she was taking salicylates in ever-increasing amounts. At this time her legs were in far worse condition than they had been with previous attacks. The malady had been diagnosed on one occasion as erythema nodosum, on another as lupus erythematosus; biopsies had been performed to diagnose the condition without success. The present attack was diagnosed as a rare peripheral vascular disease.

In view of this patient's history and physical findings, together with the fact that sclerosis and scurvy are frequently associated,[12,13] a diagnosis of scurvy was made and antiscorbutic treatment instituted. When the scurvy was under control, the vascular angle was treated in the conventional manner.[3]

The initial intravenous dose of crystalline cevitamic acid* was 100 mg., dissolved in 5 milliliters of water, and subsequent doses of 1000 mg. were given twice a week for the first month. In addition to the intravenous therapy, 300 mg. were given orally (six 50-mg. tablets), and citrus fruits to the extent of 16 to 24 ounces were included in her daily diet. Within a month marked clinical improvement was noted and the capillary fragility had reached zero.

When we felt that the danger of a relapse had passed, the intravenous therapy was reduced to once a week and the daily oral administration depended upon to keep the patient saturated. This dosage of over 300 mg. of cevitamic acid a day seemed almost unnecessarily large, since Schultzer,[15] Wright[20] and others demonstrated cures of scurvy on administration of from 40 to 60 mg. a day. However, on November 21, 1936, when she had been under treatment for 3 months, she complained of severe pretibial pain, which she stated had been present for 5 days. Examination revealed a new subperiosteal hemorrhage over the tibia of the left leg. A capillary fragility test done at this time produced 50 petechial hemorrhages in 15 minutes. The intravenous cevitamic acid therapy was increased to twice

* The crystalline cevitamic acid used in these studies was supplied through the courtesy of Merck & Co., Inc., Rahway, New Jersey.

a week, together with the daily oral administration and supplementary fruit juices, which under ordinary circumstances should have been sufficient to saturate the patient and prevent further relapse. Unfortunately, this dosage was apparently insufficient to do what was expected, for on December 4, 1936, she had a relapse more serious than the preceding one.

About noon, she developed motor and sensory aphasia and weakness of the legs. At 6 P.M., she was incoherent, unable to stand, and had twitching of the face. At 9 P.M., she recognized people but was still aphasic. She had urinary and bowel retention. Her condition was diagnosed as due to either cerebral hemorrhage, in which case scurvy was the precipitating factor, or cerebral thrombosis. In 24 hours, her right-sided paralysis was pronounced and a cord bladder added to the difficulties. In 10 days a left basal pneumonia and cystitis supervened.

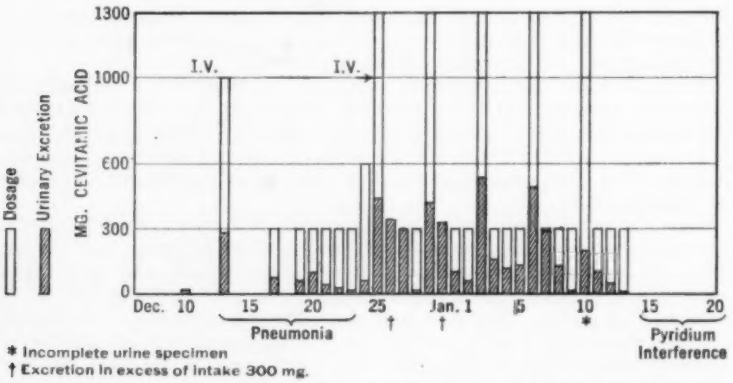

CHART 1.—Relation of urinary excretion of cevitamic acid to intake, in Case 1. (Dosage oral unless marked I. V. (intravenous). The 1300 mg. taken on 5 separate days was composed of 1000 mg. intravenously and 300 mg. orally.)

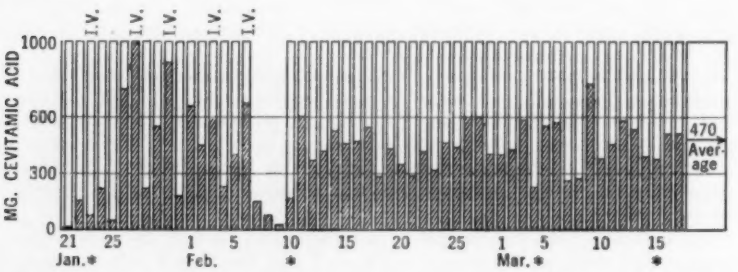

CHART 2.—Continuation of Chart 1. (For 10 months following March 17, in determinations made weekly, the average level of excretion was 470 mg. per 24 hours.)

At about this time we started determinations of the urinary vitamin C (for record covering 15 months, see Charts 1 and 2). Twenty-four-hour specimens were collected under standardized conditions,[20] namely, in amber glass bottles containing sulphuric acid and preserved at icebox temperature. They were titrated at pH 3 using a modification of Harris and Ray's[7] procedure with dichlorophenol indophenol. Pyridium used in treatment of the cystitis was found to give erroneously high vitamin C

results. A detailed description of this mode of interference has been described elsewhere.[6]

During the febrile period of pneumonia, the urinary vitamin C excretion dropped to a low point, as in the experience of Bullowa.[1] The course of the pneumonia was uneventful and is of no significance here. It required 4 months for full recovery of function of the extremities, and 5 months for complete disappearance of the motor and sensory aphasia.

Until February 6, 1937, intravenous cevitamic acid was administered 2 or 3 times a week until thrombosis of the veins of her arms made it impossible to continue this mode of therapy. The intramuscular route[10] could not be used because of the size of the dosage required and objections of the patient. Twenty-four ounces of citrus fruit juices were given on each of the next 3 days to determine if she could get enough vitamin C this way, but on the third day the excretion had dropped to 27 mg. To insure a wide margin of safety, 1000 mg. of crystalline cevitamic acid in ¼ glass of water were given orally each day, as well as at least 6 ounces of fruit juice (tomato, pineapple, grapefruit or orange) and with this medication alone the patient remained symptom-free for 10 months during which time the urinary excretion averaged 470 mg. a day.

Early in November, 1937, illness in the family caused her a great deal of concern and worry, and on December 4 (1 year after the cerebral accident) she suffered another relapse, manifested by pains in the tibiæ, edema of the legs, dry scaly skin, and an indurated area in the right calf. The capillary fragility test showed 45 petechial hemorrhages in 7½ minutes, and saturation test performed the same day gave a result of 530 mg. (of 1000 mg. intravenously) excreted in the first 5 hours. The marked fragility did not support the interpretation of normal vitamin C nutrition that the chemical test would indicate. Injections of 1000 mg. were given intravenously 3 times a week, the same dosage orally the other days, and in 2 weeks the fragility was down to 22 per 7½ minutes. At the time of writing (May, 1938) the capillary fragility is still slightly above normal, 22 per 15 minutes, although normal vitamin C saturation results are being obtained. During the last 5 months the crystalline cevitamic acid has been given orally each day, 2000 mg. one day and 1000 mg. the next, dissolved in a small quantity of water and added to the juice of 1 orange; this has been in an effort to introduce the synthetic vitamin into the stomach in a natural medium, in which there are thought to be agents that delay oxidation of this vitamin and which may also contain some factors that enhance its antiscorbutic properties. (For tabulation of above data, see Table 1.)

Comment. The problems encountered in the handling of this case have been numerous but they have shown the need for further study of precipitating factors in scurvy, of the proper evaluation of the present laboratory methods, and especially investigation of the utilizable form and fate of cevitamic acid in the human economy.

Scurvy was presumably precipitated in this individual by insufficient intake of foods rich in vitamin C, decreased absorption resulting from the generalized vascular changes of advancing age, and possibly increased excretion of the small supply in other foods by salicylate medication. Gastric achylia[16] was not present in this patient.

As the body is not able to store large amounts of vitamin C, a patient's daily requirement must be determined. Van Eekelen's[19]

investigations have indicated that the average human requirement for adults is about 60 mg. a day. This individual, however, needed more than 300 mg., which was the original dose, because almost none of this was excreted (see December 23 and 28, 1935, and January 9 and 13, 1936, in Graph 1). When 600 mg. were given (on December 24), the urine content was 50 mg. As the symptoms of scurvy reappeared on the 300 mg. dosage, and the 600 mg. permitted a little excretion, the requirement would appear to be close to 600 mg. This is also suggested by the fact that the urinary excretion on the 1000 mg. oral dose leveled off at 470 mg.

TABLE 1.—TABULATION OF DOSAGE OF VITAMIN C, THE CAPILLARY FRAGILITY COUNT, AND CLINICAL NOTES OF CASE 1.

Date.	Previous intake of vitamin C.	Capillary fragility count.	Clinical notes.
(1936)			
8–21	Rarely took citrus fruits	100 in 5 min.	First visit, tibial pain, edema of legs, numerous hemorrhagic areas on one leg.
8–26	300 mg. crystalline orally daily. 24 oz. citrus fruit juices	.....	Edema less. No pain.
8–29	100 mg. intravenously initial dose. Orally as above each day	72 in 7½ min.	No edema. Subperiosteal hemorrhage still present. No pain.
9–5	1000 mg. intravenously, b.i.w. Orally as above	45 in 15 min.	As above. Hemorrhagic areas slowly decreasing in size.
9–12	As above	34 in 15 min.	As above.
9–19	As above	29 in 15 min.	As above.
9–26	As above	0 in 15 min.	As above.
11–21	1000 mg. intravenously once weekly. Orally as above	50 in 15 min.	Tibial pain past 4 days. New large subperiosteal hemorrhage.
11–25	1000 mg. intravenously b.i.w. Orally as above	.....	Able to sleep through night without pain. Walks 3 to 4 blocks without pain. Remarkably improved.
12–4	As above	.....	Relapse, cerebral accident.
12–13	1000 mg. intravenously 3 times a week	.....	Pneumonia.
(1937)			
2–10	As above	.....	Symptom-free. Thrombosis of veins prevented further intravenous medication.
12–4	1000 mg. orally daily for past 10 months	45 in 7½ min.	Relapse, tibial pain, edema, dry skin, indurated area in calf of leg.*
12–11	1000 mg. intravenously 3 times a week. Orally on other days	35 in 7½ min.	Symptom-free.
12–18	As above	22 in 7½ min.	Symptom-free.
(1938)			
1–20	As above	18 in 7½ min.	Symptom-free.
5–10	1000 mg. and 2000 mg. orally on alternate days	22 in 15 min.	Symptom-free.

* Vitamin C saturation test—530 mg. excreted in 5 hours.

Why she suffered a return of symptoms and an increased capillary fragility after a 10 months' regimen which included 1000 mg. orally every day, is difficult to understand. The 24-hour urinary output continued to be about 500 mg., and an intravenous test dose always returned over 500 mg. in 5 hours. This apparent saturation with the anti-scorbutic vitamin is difficultly understood because intravenous administration every other day for 2 weeks was accompanied by a lowering of the fragility count. The question arises whether this last relapse may have been due to altered metabolism

caused by anxiety, or the possibility that synthetic crystalline cevitamic acid may have some fractions which cannot be utilized by this individual, thereby increasing further the dosage needed to maintain her in adequate nutritional balance, or that a deficiency had occurred of some anti-hemorrhagic factor other than vitamin C. Studies along these lines are being continued.

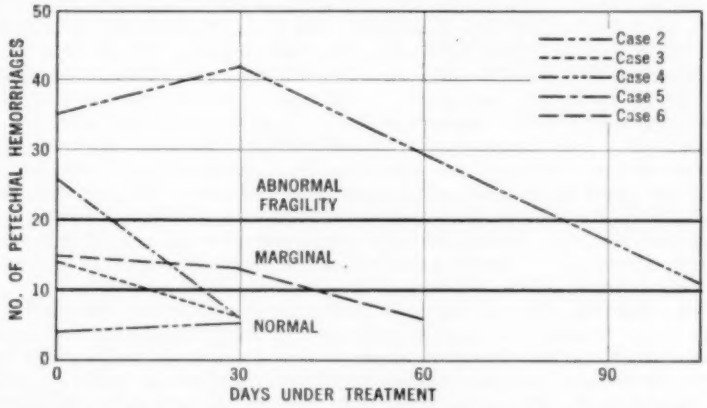

CHART 3.—The effect of cevitamic acid administered orally, 1000 mg. each day on the capillary fragility of the 5 children of Case 1.

Studies of the Patient's Children. After this patient had been under treatment for 5 months, studies were made of her 5 adult children, all of whom complained of lack of strength and frequent upper respiratory infection. They had rarely eaten citrus fruits because of a familial distaste for them. Since diagnosis of their mother's vitamin C deficiency, however, fruit juices had been taken about twice a week. Vitamin C saturation tests performed at this time showed that all were subnormal or low-normal; and with the capillary fragility test, 2 exhibited marked fragility, 2 marginal, and 1 normal. A course of treatment with large doses of crystalline cevitamic acid was followed by normal responses in every case (see Chart 3) and disappearance of symptoms.

It should be noted that these studies were made, not when the subjects were at their usual level of negligible vitamin C intake, but after they had begun to add some citrus fruits to their diet. Since the studies performed at this stage showed undersaturation of the tissues and increased capillary fragility, both of which conditions responded to vitamin C therapy, we feel inclined to attribute the symptoms of these persons to hypovitaminosis C. Presentation of their individual cases follows:

CASE 2.—Daughter, aged 21, college student, chronically fatigued, frequent attacks of upper respiratory infection, severe dysmenorrhea, joint

pains, history of rheumatic fever, mitral disease. Urine examination was normal, Roentgen ray of chest was negative, and Roentgen ray of sinuses showed moderate membranous infiltration left ethmoid, slight involvement of both antra with thickening of floor of right side.

She had an attack of rheumatic fever 13 years ago. For the next 10 years she had been incapacitated for at least 2 weeks of each year by severe pains in the ankles and knees; for all these attacks, salicylates had been administered. Three years ago tonsillectomy and extraction of 5 teeth was followed by alleviation of symptoms except for occasional mild joint pains. She had eaten almost no citrus fruit in her life. Upon examination she mentioned that she felt so tired after school that she had to take an hour's rest. She also suffered from a severe sinusitis. Blood studies revealed the red blood cells to be 4,030,000; hemoglobin (Sahli), 92%; white blood cells, 7300; stab neutrophils, 16%; segmented, 30%; large lymphocytes, 4%; small lymphocytes, 36%; monocytes, 6%; and eosinophiles, 8%. The red cells showed definite macrocytosis. The capillary fragility test produced 35 petechial hemorrhages in 15 minutes, and the vitamin C saturation result was 470 mg. (of 1000 mg. intravenously) excreted in 5 hours. The recent intake of vitamin C-containing foods had apparently saturated the tissues to a moderate extent, but had not yet effected complete repair of the perforated capillary walls.

Following oral administration of 1000 mg. of crytalline cevitamic acid daily for 1 month, the fragility test showed 42 petechial hemorrhages. After continuing this dosage for 3 months, the count fell to 11. During these same 3 months, liver was administered parenterally twice a week. At the end of this time, the blood count showed red cells to be 4,480,000; hemoglobin, 87%; white cells, 6300; stab neutrophils, 8%; segmented, 38%; monocytes, 10%, and no eosinophiles. The change from eosinophilia before treatment to the present eosinopenia as well as the increase in monocytes and lymphocytes would seem to indicate immuno-healing effort. In the red cells, the anisocytes had decreased 45%. The patient now felt so much stronger that she required no more than the night's rest.

During the summer months the crystalline form of the vitamin was discontinued, but citrus fruits were taken daily; the liver therapy was discontinued. She spent the greater part of each day in the sun on the beach. In the latter part of August, however, medical advice was sought for a pansinusitis and a recurrence of weakness. Her blood count had decreased to red blood cells, 4,080,000, and hemoglobin, 77%. With restoration of crystalline vitamin C (1000 mg. every third day) the sinus condition has been held in check and physical strength maintained.

This is another case somewhat similar to that of the mother, that links rheumatism and rheumatic fever to hypovitaminosis C. Rhinehart and his associates have reported findings suggesting that scurvy predisposes to rheumatic fever. In this individual, it is impossible to say whether there was any causative relationship between the two, but in the light of Daniels and Everson's report of increased excretion of vitamin C following administration of acetylsalicylic acid, it is interesting that the one child who had suffered from rheumatic fever and recurrent rheumatism in which salicylates was the choice of therapy, should have the highest capillary fragility, and that it should fall to normal on administration of optimum doses of vitamin C.

CASE 3.—Daughter, aged 26, complained of extreme fatigue, nervousness, poor circulation in the extremities, loss of appetite, sinusitis. Urine and chemical blood examinations were normal, physical examination and Roentgen ray of chest, negative.

Because of marked distaste for citrus fruits, this patient had not taken any "since she could remember." One year before, during a cold, she had tried to eat an orange but suffered an upset stomach, possibly as a psychological or allergic reaction. When her mother's vitamin C deficiency was diagnosed, she managed to drink the juice of 3 oranges a day for 3 days when urticaria developed on the face. When the fruit was withdrawn, this disturbance disappeared. Later all citrus fruits were slowly added to her diet with no reaction.

When examined here, the blood count showed a hemoglobin (Sahli) of 72%, and red blood cells, 4,080,000. The capillary fragility test produced 14 petechial hemorrhages in 15 minutes, and in a study of vitamin C saturation, 390 mg. were excreted in 5 hours. After taking crystalline cevitamic acid, 1000 mg. daily for 1 month, the capillary fragility count fell to 6.

For the last 2 years she had been under medical care for secondary anemia. Virtually all this time liver and iron pills had been taken, but the hemoglobin stayed between 67 and 72%, and the red cell count between 3,500,000 and 3,800,000. A course of ultraviolet treatments was ineffective. When liver was administered parenterally twice a week for 12 weeks, the hemoglobin remained the same but the red cell count rose to 4,300,000. After 300 mg. crystalline cevitamic acid (six 50-mg. tablets) had been taken together with tablets of a liver and iron preparation daily for 6 weeks, the hemoglobin rose to 82% and the red cell count to 4,620,000. At this time the patient felt vigor unknown for some years. Plenty of fruit juices were taken with the liver and iron. In less than 2 months, however, a return of weakness was explained by a hemoglobin of 76 and red cell count of 4,190,000. Restoration of crystalline cevitamic acid was accompanied by a return of strength as well as improvement of the red count within a month to 4,420,000.

This case seems to represent the type of anemia, described by Mettier and Minot[12] which is responsive, not to liver and iron therapy alone, but to adequate vitamin C nutrition.

CASE 4.—Daughter, aged 29, fatigued, frequent upper respiratory infections, recurrent painful ulcers on the mucous membranes of the cheeks, gums and tongue.

This is the only member of the family whose capillary fragility was within the normal range, namely, 4 petechial hemorrhages in 15 minutes. Her vitamin C saturation result of 400 mg. (of 1000 mg.) excreted in 5 hours, however, was borderline. A blood count showed the hemoglobin (Sahli) to be 78%, the red blood cells, 3,840,000, and the white blood cells, 6100. The red cells showed macrocytosis and microcytosis. Because of the questionable state of vitamin C nutrition indicated by the small response to the test dose, crystalline vitamin C was prescribed as well as parenteral liver injections. The liver was given biweekly for 12 weeks and the cevitamic acid, 1000 mg. orally each day for 1 month and biweekly thereafter. At the end of this course, the hemoglobin had risen to 95, the red cells to 4,250,000 and the white cells to 9200. Anisocytosis of the red cells had decreased 50%.

The liver and crystalline cevitamic acid were discontinued and citrus fruits depended upon to maintain adequate vitamin C nutrition. After 6 months during which the ulcers appeared less frequently, they finally

ceased to recur. In the past year she has maintained a high standard of health, avoiding colds for the first time in several years.

It is difficult to say whether this recovery was brought about by the liver or the vitamin C, but considering her history of very low vitamin C intake, and the fact that she has remained symptom-free since the liver therapy was discontinued, on a diet containing adequate vitamin C, there seems to be a definite possibility that her case was partly due to hypovitaminosis C.

CASE 5.—Daughter, aged 32, complained of fatigue, irritability, and frequent upper respiratory infection.

This patient had received two courses of iron injections during the past 5 years for a persistent anemia in which the hemoglobin fluctuated between 60 and 70%. Each winter had brought on such decrease in strength that she had had to leave her work for a week or more and go to a warmer climate. When examined here, her blood count revealed a red cell count of 3,760,000, a hemoglobin (Sahli) of 88%, and moderate macrocytosis. In a test of vitamin C saturation, 460 mg. (of 1000 mg. intravenously) were excreted in 5 hours. Although, according to this result, her tissues would seem to have achieved a slight degree of saturation by the recent addition of vitamin C-containing foods to her diet, the capillary fragility count was 26 petechial hemorrhages in 15 minutes. Oral administration of 1000 mg. of crystalline cevitamic acid each day for 1 month resulted in a decrease of the fragility count to 6.

After liver had been given parenterally twice a week for 3 months, accompanied by large doses of the crystalline vitamin (1000 mg. biweekly, orally) the red cell count was 4,390,000, with a decrease in the number of anisocytes. In the year since then, nothing has been prescribed except adequate fruit juices, and yet vigorous health has been maintained. She has had no colds for the first winter in several years.

This more thorough recovery than that of other years may have been brought about by the improved vitamin C nutrition. In view of her history of very low citrus fruit intake and her marked capillary fragility that became normal after a course of cevitamic acid therapy, it would appear probable that the heretofore chronic anemia may have been largely due to deficiency of vitamin C. Studies of Minot and Mettier[12,13] have shown that some anemia is caused, not so much by lack of the metallic elements, iron and copper, as by subminimal vitamin C nutrition.

CASE 6.—Son, aged 34, excessive fatigue, bleeding gums, chronic sinusitis. The blood count of this patient seemed normal, showing a hemoglobin (Sahli) of 92% and a red cell count of 4,740,000, but he complained of feeling extremely tired by mid-afternoon and of requiring a great deal of sleep. His gums bled very often, and he had a chronic sinusitis. On examination, the capillary fragility count was 15 petechial hemorrhages in 15 minutes, and the vitamin C saturation result was 375 mg. (of 1000 mg. intravenously) excreted in 5 hours.

Since the capillary fragility was borderline and the saturation result subnormal, even though he had lately added citrus fruits to his diet, crystalline cevitamic acid (1000 mg. orally each day) was prescribed. After 1 month the fragility count was 13, and after another month it had fallen

to 6. The bleeding of the gums ceased, and has not recurred in the past year during which fruit juices have been taken daily. The sinusitis has subsided to a great extent and there is no longer the feeling of excessive fatigue.

The combination of symptoms and clinical observations suggestive of vitamin C deficiency, all of which became normal on administration of the crystalline form of the vitamin, point to the likelihood that his vague illness was caused by hypovitaminosis C.

As in the cases of the other children, the recent intake of vitamin C-containing foods was no doubt responsible for the finding of a borderline rather than a marked deficiency of the vitamin.

Summary. The causes, symptoms and criteria for the diagnosis of scurvy are reviewed. The case reports of a mother and 5 children in good financial circumstances present varying degrees of hypovitaminosis C, resulting from distaste for and consequent restriction of foods rich in this vitamin.

Determinations of cevitamic acid content of the body fluids by the present laboratory methods require careful evaluation, and cannot take the place of thorough clinical study.

Since the principal patient described required about 500 mg. of crystalline cevitamic acid intravenously daily to bring about chemical saturation and disappearance of symptoms, and later relapsed while receiving 1000 mg. orally each day, the question arises whether this is due to a metabolic peculiarity of this individual which changes the vitamin into a non-antiscorbutic form, or whether the potency of the synthetic substance may be altered by mechanical handling, storage conditions, or as yet unrecognized factors in the methods of administration, or thirdly, whether a deficiency of some factor other than synthetic vitamin C produced her scorbutic-like syndrome.

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DETERMINATION OF THE CODEHYDROGENASES I AND II (COZYMASE) IN THE BLOOD OF DIABETICS IN SEVERE ACIDOSIS.*

By Richard W. Vilter, M.D.,
ASSISTANT RESIDENT, DEPARTMENT OF INTERNAL MEDICINE, CINCINNATI GENERAL HOSPITAL,

Sue Potter Vilter, M.A.,
DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CINCINNATI,
AND
Tom D. Spies, M.D.,
ASSOCIATE PROFESSOR OF MEDICINE, DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

(From the Department of Internal Medicine and Biochemistry, University of Cincinnati College of Medicine.)

Observations on a large series of pellagrins during the past 8 years have shown that not infrequently clinical pellagra develops in patients with diabetes mellitus, and that pellagrins in acute relapse rapidly become worse when restricted to diets of large amounts of glucose. Pellagrins in relapse excrete in the urine increased amounts of an ether-soluble substance, or substances, giving the color of porphyrin in 25% HCl. This substance disappears promptly from the urine following the administration of nicotinic acid and reappears when nicotinic acid therapy is discontinued.[6] We used the same method to test the urine from a patient in diabetic coma but with no clinical evidence of pellagra and the results were similar to those observed in pellagrins.[5] Recent observations by Vilter, Vilter and Spies,[8a,b] showing that the blood from patients with chronic leukemia and from pellagrins in relapse contains less cozymase and coferment than normal blood and that the content of these coenzymes in the blood of pellagrins can be raised by oral administration of nicotinic acid, led us to apply the same method in the study of the blood from 3 cases of diabetes mellitus. The present report is concerned with this study.

Method. Five cultures of *B. influenzæ* and *B. parainfluenzæ* were carried on chocolate agar slants, and studied in broth sub-cultures. The broth was prepared with 2% Difco proteose-peptone, 0.6% salt and 2% human blood. This medium, pH 7.6 was heated to 95° C. and filtered; a portion was sterilized by filtration through a Seitz filter and another portion was autoclaved. As was expected, the portion of autoclaved medium was found not to support growth of those members of the influenza group studied, since cozymase, factor V, is destroyed by autoclaving. The unautoclaved medium, in contrast, provided luxuriant growth of these organisms, as has been shown previously by Davis[1] and by Thjötta and Avery.[7]

The procedure was as follows: 1 cc. of venous blood was added to 19 cc. of sterile distilled water and heated in a water-bath at 85° C. until the color of the solution became brown. The solution was cooled, and after the

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addition of 1 to 2 drops of sterile N/10 HCl was centrifuged. The supernatant fluid was then added to tubes of autoclaved peptone broth so that the final dilutions of blood added to the prepared medium represented volumes ratios of 1/1000, 1/2000, 1/4000, 1/8000 and 1/12,000. The blood was heated at 85° C. so the proteins could be centrifuged out, and so the labile inhibitory substance in the serum, described by Rivers and Leuschner[3] would be partially or totally destroyed.*

This method has been found to be extremely sensitive. In controlled experiments, the addition of a solution of cozymase to autoclaved broth produced heavy growth at a concentration of 1 part per 100 million. Moreover, the sterility of the media and of all the reagents was proved by control tubes set up with each experiment.

Selection of Cases. Three patients admitted to the Cincinnati General Hospital in severe diabetic acidosis (blood carbon dioxide combining power less than 20 vol. %) were selected for study. Case 1 (J. B.), a white boy, 14 years of age, without previous knowledge of diabetes, had been eating large quantities of an adequate and varied diet until he became drowsy the day of entry. Case 2 (E. M.), a negress, had been vomiting for 8 days before admission. Case 3 (E. W.), a negress, had taken no insulin and eaten little food for a week before entry since she had been incapacitated by an acute upper respiratory infection. In none of the cases was there clinical evidence of pellagra nor of severe systemic disease other than diabetes mellitus. Each patient made a satisfactory recovery following routine therapy, consisting of parenteral administration of large quantities of insulin, physiologic saline and a 10% glucose solution. In each case the blood of a member of the hospital staff served as a control for the diabetic blood under investigation.

Observations. As shown in Table 1, the admission blood of the cases suffering from severe diabetic acidosis, when inoculated with loop transfers from a 12-hour culture of *B. influenzæ*, supported growth of this organism in dilutions of 1/2000 or less. In contrast, the blood of the control series invariably supported growth in dilutions of 1/8000 or more.

Following excellent responses to the routine diabetic therapy described above, determinations of growth factor present in the blood were repeated within an interval of 10 days. The blood of Case 1 was found to support growth of the influenza bacillus in dilutions up to and including 1/8000. Similarly, the blood of Case 3, after the much shorter interval of 3 days, supported growth well in the 1/4000 dilutions.

Case 2 was maintained for 3 days following return of consciousness on a diet of orange juice and egg white. During the last 48 hours of this period, she was given orally 500 mg. of nicotinic acid, and then her blood was retested for growth factor. Although her blood at the outset, supported minimal influenza growth in the 1/1000 dilution only, following nicotinic acid therapy, *B. influenzæ* grew

* Dr. H. I. Kohn (Biochem. J., **32**, 2075, 1938) has published recently a method similar to ours.

well in the 1/8000 blood dilution. Likewise, increased amounts of prophyrin or substances resembling porphyrin were found in her urine before nicotinic acid therapy and disappeared after the drug had been administered.

TABLE 1.—TWENTY-FOUR-HOUR GROWTH OF B. INFLUENZÆ IN DILUTIONS OF BLOOD IN AUTOCLAVED PEPTONE-BLOOD BROTH.

Diabetic patients in coma.		Dilutions of blood. 1/1000.	1/2000.	1/4000.	1/8000.	1/12,000.	R.B.C.	Nicotinic acid given, mg.	Porphyrin-like substance in urine.
Case 1 (J. B.)	12/12/38	+	±	−	−	−	5.9	..	Not done.
Case 2 (E. M.)	12/23/38	±	−	−	−	−	5.5	..	Positive.
Case 3 (E. W.)	12/31/38	++	±	−	−	−	..	..	Negative.
+18 nicotinic amide in each tube		++	−	−					
+18 nicotinic amide and 1 cozymase in each tube		+++	+++	+++					
+1 cozymase in each tube		+++	+++	+++					
Same diabetic patients after routine treatment and subsequent recovery.									
Case 1 (J. B.)	12/22/38	++++	+++	++	±	−	4.8	..	Not done.
Case 2 (E. M.)	12/26/38	+++	++	+	+	−	4.74	500	Negative.
Case 3 (E. W.)	1/3/39	+++	++	++	−	−	4.7	..	Negative.
Normal cases used as control to viability of culture for each of above cases.									
J. F.	12/12/38	++++	+++	++	+	±			
W. F.	12/23/38	++++	+++	++	±	±			
S. P. V.	12/31/38	++++	+++	++	±	−			
W. F.	12/22/38	++++	+++	++	±	±			
S. P. V.	12/26/38	++++	+++	++	±	±			
R. W. V.	1/3/39	++++	+++	++	+	−			

NOTE.—The extent of growth was interpreted as follows: ++++ = very heavy; +++ = heavy; ++ = moderately dense; + = light; ± = just perceptible; − = no growth. The controls of the culture in autoclaved medium without added blood were negative in each case. The sterility of the blood which was added was also established.

Lwoff and Lwoff[2] have shown that bacilli of the influenza group require a codehydrogenase for growth, and are unable to synthesize it from its components, nicotinic acid amide, adenylic acid, ribose and phosphoric acid. In a previous paper[3a] it has been shown that such a factor is decreased in the blood of pellagrins in relapse and is restored by administration of nicotinic acid. Whether a similar

restoration could be aided by administering the other components of the enzyme through a mass action like effect is plausible but as yet untried. The evidence advanced above indicates that a similar factor is deficient in the blood of diabetics in severe acidosis. That this factor is cozymase is supported by the following evidence.

A sample of cozymase* was dissolved in distilled water, so that 1 cc. contained 10 γ. Three series of autoclaved tubed media containing 1/1000, 1/2000 and 1/4000 dilutions of admission blood from Case 3 were prepared. Eighteen γ nicotinic acid amide were added to each tube of the first series, the same amount of nicotinic acid amide and 1 γ cozymase to each tube in the second series, and 1 γ cozymase alone to each tube of the third series. The results were conclusive. Those tubes containing cozymase supported luxuriant growth in all dilutions, while those containing nicotinic acid amide alone were equivalent to the untreated diabetic blood, for growth took place only in the 1/1000 dilution. Control tubes showed that the cozymase solution was sterile after filtration and that it alone in concentrations of 1 part in 100,000,000 would support growth in the autoclaved media.

Conclusions. 1. This report shows that the blood of patients suffering from severe diabetic acidosis supports the growth of *B. influenzæ* to much less extent than does the blood of normal individuals or the same diabetic when regulated or given doses of nicotinic acid.

2. The codehydrogenase I (cozymase) when added to such deficient blood or to autoclaved media without blood supports luxuriant growth of the influenza bacillus, although nicotinic acid amide shows no such growth stimulation.

3. These observations show that not only is codehydrogenase I deficient in the blood of pellagrins in relapse, but also in the blood of diabetics in severe acidosis, and support the hypothesis that the therapeutic effect of nicotinic acid depends upon the synthesis in the body of nicotinic acid nucleotide and finally of a codehydrogenase.

(Note added to the proof by the author). Spies and Koch[4] have shown that brewers' yeast (Anheuser-Busch, Inc., The Harris Laboratories, Mead Johnson & Co.) and liver extract (Lilly No. 343) both contain cozymase as evidenced by their ability to support growth of *B. influenzæ* under the conditions of the method described in this study. Corn meal, which is one of the major constituents of the pellagra-producing diet, also supports growth to some extent, but not nearly so well as does the yeast or liver extract which are anti-pellagric materials. Spies and Koch have shown that 20 normal persons, carefully chosen because they were in good health and were known to eat adequate amounts of a well-balanced diet, excreted cozymase in the urine. In these 20 cases dilutions of 1 to 100, and often dilutions of 1 to 1000, supported growth of the *B. influenzæ*. Repeated examinations of the urine of a patient (C. K.) with chronic lymphatic leukemia showed that it supported growth of the *B. influenzæ* in dilutions of only 1 to 10, and her blood only in dilutions of 1 to 100. The administration of nicotinic acid, 500 mg. daily, by mouth, was followed by a transient increase in cozymase concentration in the blood and urine. Keeping the nicotinic acid intake constant, the addition of 100 gm. of dry brewers' yeast, by mouth, produced a definite increase to where the blood would grow *B. influenzæ* in dilutions of 1 to 2000. After keeping the nicotinic acid and yeast therapy constant for several days, an injection of 20 mg. of riboflavin in sterile physiologic solution of sodium

* Obtained through the courtesy of Dr. Hans Molitor of Merck & Co.

chloride was given. This was followed by a spectacular increase in growth supporting activity through the 1 to 12,000 dilutions. Associated with this increase in cozymase content of the blood was a feeling of well-being, and the patient was able to get out of bed and aid in caring for other patients, despite the fact that her red cell count remained around 2,300,000. It is too early to know whether the blood cells are affected following elevation of cozymase in the blood, but persons having as low a concentration of cozymase as this patient might reasonably be expected to improve following a rise of cozymase content in the blood and tissues. On numerous occasions cozymase has been added to various inoculated tubes and invariably it has supported growth of these bacteria, indicating that the variation from the normal controls is the result of a deficiency of cozymase, or some substance which acts similarly, rather than some hypothetical inhibiting substance.

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THE RELATION OF POTASSIUM TO PERIODIC FAMILY PARALYSIS.

By George D. Gammon, M.D.,* †
ASSOCIATE IN NEUROLOGY; INSTRUCTOR IN MEDICINE,
J. Harold Austin, M.D.,
PROFESSOR OF RESEARCH MEDICINE,
Margaret D. Blithe, M.A.,
AND
C. Graham Reid, M.D.,
SMITH, KLINE AND FRENCH FELLOW, GASTRO-INTESTINAL SECTION,
PHILADELPHIA, PA.

(From the Institute of Neurology, the Medical Clinic of the Hospital and John Herr Musser Department of Research Medicine, University of Pennsylvania.)

In this paper we present data which were gathered on a patient with periodic family paralysis during the past 24 months in an effort to clarify the relationship of postassium (K) to the attacks of weakness in this disease. One of us[4] has previously summarized elsewhere some of the results and discussed the problem in the light of recent literature. Older work had suggested that K citrate[9]‡ would sometimes shorten an attack, and Holtzapple[6] had relieved seizures with KBr, although he attributed the result to the bromide rather than to the K. Japanese investigators[10,12] had been able to induce seizures with adrenalin, sugar and insulin, all of which lower serum K. There was thus clear indication that K was in some way connected with the attacks. We found early that K salts in sufficient quantity would promptly cure the weakness, and that during

* Godey and Seeger Fellow. † Supported by Kirby-McCarthy Fund.
‡ We wish to express thanks to Dr. W. S. McCann, Rochester, N. Y., for calling our attention to this reference; he examined a grandchild of this patient who still takes K citrate for the seizures.

attacks serum K was low. Aitken *et al.*[1] independently made the same observations and published their results prior to ours.

The immediate problem was to establish a more exact relationship between the lowered serum K and the muscular weakness and to seek the reason K fell in the attacks.

Clinical Abstract. The patient, a male, aged 16, suffered from the type of the disease in which attacks occur almost daily. The long period of observation served to establish the characteristics of the spontaneous seizures and enabled us better to judge the effects of various experimental and therapeutic procedures.

The attacks begin almost invariably in the early morning hours between 3 and 7 A.M. during sleep, and last into midmorning, or if severe, until evening. Recovery, once initiated, is prompt and complete. The body musculature suffers unequally; sometimes the arms are more affected, at other times the legs. Extensor muscles are usually weaker than the flexors. During the attacks the muscles are flaccid, reflexes are abolished, and the response to electrical stimulation is decreased or unobtainable. No sensory changes develop.

In spite of the severity of the disease the bulk and development of the muscles is excellent. The external genitalia are normal and sexual function is established, but the testicles are quite small. No other physical defects are present. Routine studies of blood and urine are normal.

The father is the only other member of the family with the disease; two younger siblings are healthy. The father was studied by Dr. Wm. G. Spiller and Dr. J. W. McConnell of Philadelphia in the earlier seizures; his attacks were less frequent and more prolonged than his son's, and have decreased in frequency as he has grown older. K salts will also relieve his weakness.

Methods. Serum and feces were analyzed for K by the chlorplatinate method of Hald,[5] and urine by the same method with preliminary ashing with thorium nitrate after Strauss.[11] Samples were ashed and analyzed in triplicate; blanks and recoveries of added K were run daily. All data reported are based on samples ashed in silica containers; earlier analyses when ashing was performed in Pyrex were discarded because of irregularities in the measurements. The K estimations have a standard error of 2%.

Blood samples were taken without anticoagulant in centrifuge tubes and separated within 15 minutes. During the study of K excretion, a weighed diet calculated to contain not quite 3 gm. K per day was furnished in 3 different menus fed in recurring 3-day cycles.* Approximately equal quantities of distilled water were taken daily. Urine was collected at intervals selected for each experiment.

Relation of the Serum K Level to the Attack. During severe spontaneous seizures, the serum K level has fallen by as much as 30%. These observations agree with the findings of Aitken *et al.*[1] But in milder attacks the fall has been much less, at times only 5 to 10%, figures of the order of 4.79 m.eq. per L. being obtained during the seizure. In attacks induced by various means this relationship between severity of weakness and degree of lowering of serum K has not been so evident; thus after adrenalin the fall in serum K may be considerable even with a mild attack, while severe seizures set up by drinking large quantities of water may be accompanied by only a slight fall in K. In one experiment, November 20, 1937, the patient was well with a serum K of 5.44 m.eq. per L.; 2 hours

* We wish to express our thanks to Miss Marion Mowbray and Miss Eleanor Erickson, Dietitians in the Hospital.

later adrenalin (minims 10, 1 to 1000, hypodermically) was given which produced a mild attack within 20 minutes. In 45 minutes the patient could get out of a chair only with assistance; serum K had fallen to 3.73. When spontaneous complete recovery had occurred about an hour after the injection, the K had risen only to 4.15, a figure lower than has occurred in some mild spontaneous seizures. In a severe attack after a water diuresis, there was little fall in serum K (Fig. 1). The subject was normal with serum K of 5.44 m.eq. per L., showed slight weakness at 5.12, and was unable to move off the bed at a level of 5.00.

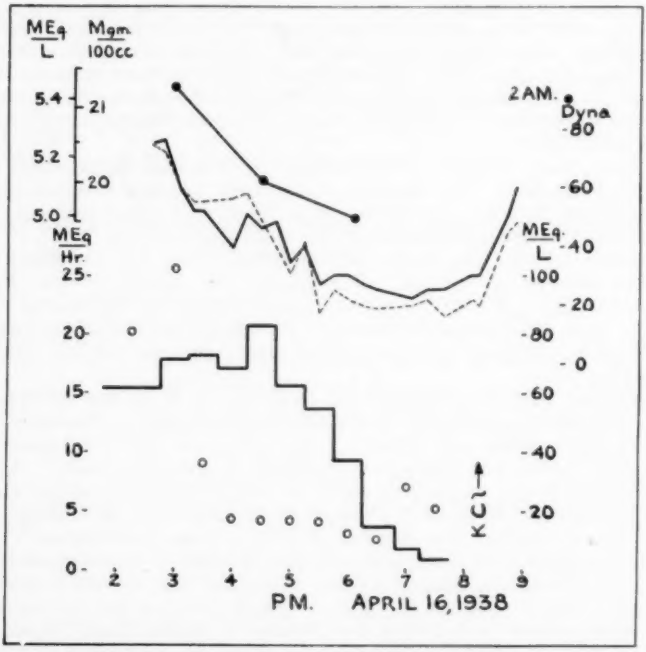

FIG. 1.—Effect of water diuresis following a large dose of K, in lowering serum K and inducing an attack. ●——● Serum K; against scale at left. ——— left hand; ---------- right hand; dynamometer record of maximum grasp; read against scale on right. Columns at base show K excretion in urine; read against scale on left. ○ K concentration in urine; read against scale on right.

There is thus no constant level of serum K associated with transition from strength to weakness nor from weakness to strength; however, when the curve of K has been followed, the attack has developed with a falling, and the recovery ensued on a rising, serum K.

Potassium Excretion in Relation to Seizures. Reference has already been made to the fact that seizures could be induced by water diuresis; in each of three trials the attempt was successful. So far as we are aware this method of setting up an attack has not been observed before. It was thus of interest to determine whether the diuresis

led to the elimination of K in large quantities prior to the development of weakness. This was found to be the case, and accompanying the attack, as we have stated, serum K fell slightly.

In one trial, 6 glasses of water in 1 hour raised the potassium excretion rate from 9.9 m.eq. per hour to 16.5, five times the usual daytime excretion rate. When, after 2 hours, 29 m.eq. of K had been excreted in the urine, weakness began to develop.

The experiment performed April 16, 1938, is recorded in Figure 1. The patient had taken at noon 5 gm. KCl to relieve a severe attack; by 1 P.M. he was well. At 2.50 P.M. vigorous water intake was started; 350 cc. were consumed each half hour until 5.45 P.M., a total of 2.6 L. Weakness promptly developed as indicated by the dynamometer readings, and became so severe that by 6.15 he was just able to sit, and by 8.10 he could no longer rise to a sitting position. Thus a full attack developed despite the large dose of KCl at noon. The attack was terminated by another dose of KCl at 8.15; within 45 minutes his usual strength had returned. During the diuresis 73 m.eq. K (1.9 gm.) had been lost in $3\frac{1}{3}$ hours. Associated with this depletion of K, a severe weakness developed and the serum K fell from 5.44 m.eq. to 5.00.

As it was possible to induce attacks by means of a diuresis, we examined the urine prior to spontaneous seizures to see if a similar outpouring of K preceded the natural attacks. The patient was placed on the diet described above, and urinary and fecal K determined. The night urine was fractionated to obtain the periods preceding seizures. Fecal K was only followed long enough to determine that it varied little and was about 8 m.eq. per day. Urinary excretion was followed several weeks. A record of 5 consecutive days in Figure 2 is representative. The patient was in approximate balance, eliminating 53.5 m.eq. K per day. (The diet presumably contained 61 m.eq. daily.) A control subject on the same diet excreted 58.7 m.eq. per day (Fig. 3).

From the record it can be seen that K excretion at night was no higher preceding the day of an attack than preceding a normal day; nor was it greater before a severe seizure than a mild one. There is thus no evidence of a spontaneous K diuresis prior to the attack. During the seizure itself, K excretion falls. From these observations we may infer that the K which leaves the serum during the weakness is not eliminated, but probably enters other body fluids or tissues.

The daily rhythm of excretion of K shows there is a rapid elimination during the period of absorption from the gastro-intestinal tract, while at night excretion falls to low levels. The same rhythm is seen in the control (Fig. 3), but is exaggerated in the patient. The ratio of highest to lowest rate of excretion in the control was 5; in the patient, 15.

K Therapy. The attacks of weakness, as we have already stated, can be promptly terminated by K salts in sufficient quantity. In our patient, 2 to 5 gm. KCl by mouth were required, depending

on the severity of the attack. Other K salts were also effective but less useful because of undesirable side actions. Sodium salts, NaCl

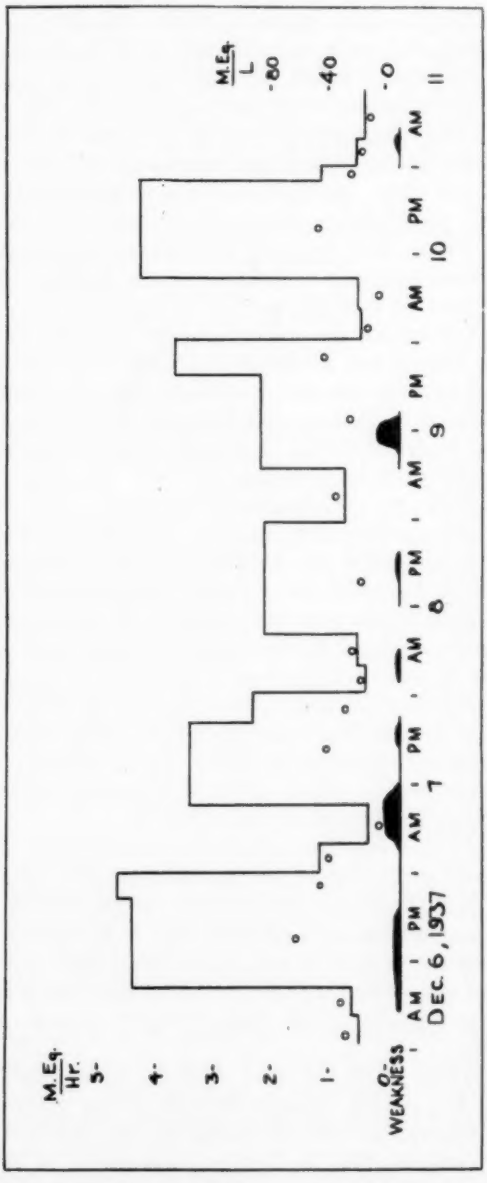

FIG. 2.—Patient R. E. ◦ K concentrations in urine; scale on right. Block columns: K excretion rate in urine; scale on left. Black patches at base indicate clinical weakness of legs and arms. Moderately severe attacks December 7 and 9. Adrenalin administered December 8 at noon, producing very slight attack.

and $NaHCO_3$, were ineffectual as were creatin hydrate (15 gm. by mouth) and prostigmin (1.5 mg. hypodermically).

From the excretion studies it was clear that K given during the day would be rapidly eliminated and hence would not prevent noc-

turnal seizures. When we gave KCl at 2 A.M. (4 gm. together with a soup to prevent rapid absorption) we were able to keep the patient relatively free from attacks. Previous efforts to prevent night seizures by administration of K during the day had failed.

Discussion. It appears to us from the studies of this disease that the lowered serum K is not *per se* an adequate explanation of the weakness; for attacks have occurred with serum K within 10% of normal value and at a level which causes no weakness in normal subjects. Furthermore, McEachern[7] has observed partial remission from an attack after small doses of K but without any associated elevation of the lowered serum K.

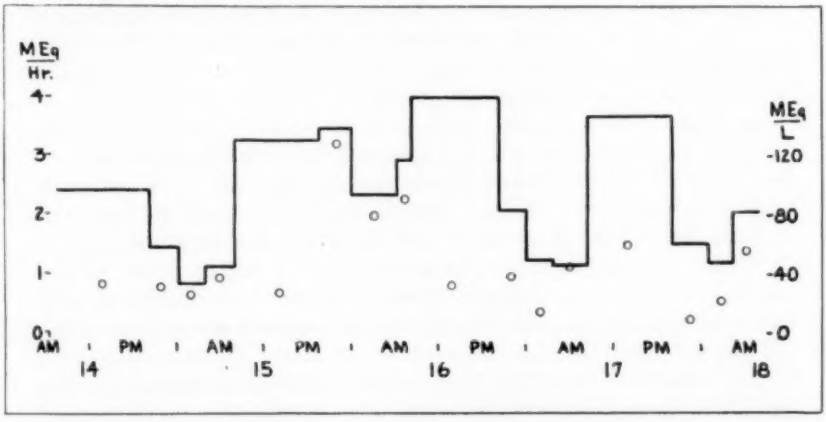

FIG. 3.—Control G. G. ○ K concentrations in urine; scale on right. Block columns: K excretion rate in urine; scale on left.

We next inquire whether the lowered serum K of the severer attack is preceded by excessive loss of K by excretion. In our experiment with water diuresis this is clearly the case. In the spontaneous seizures, however, our data give no evidence of exaggerated loss of K, either before or during the seizure.* Consequently, the fall of serum K in these attacks must result from transfer of K from serum to some other tissue or fluid, the site of which cannot be definitely assigned.

It may be that the K passes from serum to the disordered muscle in response to an abnormal demand for K, arising in the muscle as the attack comes on, and if so the fall in serum K is to be viewed as secondary or compensatory. By this hypothesis, as the attack develops, K is drawn from the available sources; when these fail, serum K falls. The more severe and more extensive the attack,

* Since this paper was written Allott and McArdle[2] have published a study in which they found no evidence of a K diuresis preceding the attack; and Ferrebee, Atchley and Loeb[3] have read a paper before the Society for Clinical Investigation reporting in a similar case low serum K during attacks, no correlation with serum glucose or phosphate, marked drop in urinary potassium excretion during an attack, with following compensating increase in potassium excretion, increase of creatinuria during an attack, and alleviation and prevention of attacks from potassium chloride by mouth.

the greater would be the expected fall in serum K. When, as sometimes, the attack is confined to a few muscles, little or no fall in serum K might be expected. Attacks would be more frequent when the compensatory sources of K were depleted; consequently, attacks would tend to occur late in the night when no K was being absorbed from the gut or when, as after water diuresis, the reserve of K had been excreted. The tendency of adrenalin and glucose and insulin to bring on an attack may result from changes induced which are manifest in the transfer of serum K to the peripheral tissues.[8] The relief of seizures by administration of K salts would be expected.

The various factors which are known to induce or relieve attacks can under this hypothesis be related. But as to the nature of the primary disturbance in the muscle, which creates the demand for K, there is at present no direct evidence.

Summary. In a patient with periodic family paralysis we observed a rapid loss through the urine of K absorbed from the gastrointestinal tract; in the late hours of the night the rate of K excretion was unusually low. Water diuresis rapidly washed K from the patient, with a fall in serum K and the development of a seizure.

Attacks of weakness were associated with a falling serum K and recovery with rising values. There was, however, no fixed level below which weakness developed. K salts were of use in preventing as well as curing seizures.

The attacks of weakness appeared to develop at times when the supply of K available for absorption or redistribution was depleted.

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SOME DIFFERENT TYPES OF ESSENTIAL HYPERTENSION: THEIR COURSE AND PROGNOSIS.

By Norman M. Keith, M.D.,
DIVISION OF MEDICINE,
Henry P. Wagener, M.D.,
SECTION ON OPHTHALMOLOGY,
AND
Nelson W. Barker, M.D.,
DIVISION OF MEDICINE, THE MAYO CLINIC, ROCHESTER, MINN.

Since the recognition of the clinical syndrome of essential hypertension 40 years ago, much has been learned in regard to its abnormal physiology and ultimate course. However, the question of etiology

still baffles investigators and, until its cause or causes are established, physicians should try to group their cases by the best available methods. Allbutt,[1] in 1896, believed that the outlook for some of these patients was good for many years. As the recognition of cases increased in number and as the use of the Riva-Rocci[14] sphygmomanometer became general, many physicians, including Janeway,[6] gradually realized that there were variations in the severity of the condition. This fact led Volhard and Fahr,[16] in 1914, to speak of benign and malignant forms of the disease. Two of us began our joint study of our more serious cases in 1920 and, in 1928,[9] reported the detailed findings in 81 cases of what was termed "the malignant hypertension syndrome." Many of the cases differed from the malignant hypertension of Volhard and Fahr and the malignant nephrosclerosis of Fahr,[3a] in that a diagnosis frequently was made before there was serious impairment of retinal, cerebral, cardiac, and renal functions.

With further study, it became obvious that there were many cases of essential hypertension which did not belong in this group of rapidly progressive cases and could not be termed cases of benign or simple hyperpiesia. Gradually, a group could be identified in which the presence of mild vasospastic retinitis was an important diagnostic feature. The course was less rapid and remission of symptoms sometimes occurred. We have identified another group, the salient features of which are more marked hypertension and more distinct narrowing and sclerosis of the retinal arterioles than encountered in the benign cases, and yet there is no demonstrable break in retinal, cerebral, cardiac, or renal functions.[7,8]

To avoid confusing descriptive terms, the groups have been given numbers. We have considered the usual benign cases as belonging to Group 1; those of more marked hypertension, presenting few untoward symptoms, without retinitis as belonging to Group 2; those of mild vasospastic retinitis as belonging to Group 3, and those revealing the so-called malignant hypertension syndrome as belonging to Group 4.

Kernohan,[9] in examination of pathologic material obtained at necropsy in our cases of Group 4, found that changes in the arterioles were often widespread throughout the body. Similar findings since then have been reported by Scott, Seecof and Hill,[15] Pilcher and Schwab,[13] and Moritz and Oldt.[12] These facts suggested a study of the arterioles in tissue obtained by biopsy which would give information concerning the peripheral arterioles during life among cases of the four groups. Skeletal muscle was chosen because it represented a large portion of the weight of the body and was less subject to local disease which might involve the blood-vessels. The pectoralis major muscle was selected because of its accessibility.[8,10] This study began in November, 1927, and, between that date and August, 1932, a period of 5 years, the arterioles of

muscle obtained from 138 patients who had hypertensive disease were examined. In addition to this histologic study of the arterioles of muscle in 138 cases belonging to the four groups, a follow-up record was kept of every case up to 1937, or approximately 9 years from the time when the first patient was examined and 5 years from the time when the last patient was examined. A follow-up study of the 81 cases belonging to Group 4, begun in 1920 and reported in 1928,[9] has been continued so that now we have accurate data on the course of 146 cases of Group 4 and 219 cases belonging to all groups* (Table 1).

TABLE 1.—DATA AT TIME OF FIRST EXAMINATION.

Hypertension, group.	No. of patients.			Age, years.	
	Male.	Female.	Total.	Range.	Mean.
1	7	3	10	30–65	55
2	14	12	26	21–59	41
3	22	15	37	22–57	42
4	99	47	146*	8–64	40
Total	142	77	219		

* Biopsy of muscle was carried out in 65 cases.

Groups. *Diffuse Arteriolar Disease With Hypertension,† Group 1.* Many of the cases described by Allbutt,[1] Janeway,[6] and others as cases of hyperpiesia or essential hypertension belong in this group. The hypertension can be of long duration without causing symptoms and without impairing general health. Cardiac and renal functions continue to be adequate and changes in the retinal vessels are minimal. Albuminuria may be of a slight degree or may be absent, and, in spite of the gradual development of hypertrophy of the heart, electrocardiologic examinations may give evidence of normal findings for many years. The hypertension as a rule does not rise to extreme heights, and among many individuals falls to normal levels during sleep. With moderate protection of the vascular system, the prognosis is usually good. Happily, the majority of cases encountered in practice fall into this group. As a rule, we found few anatomic changes in the arterioles of muscles so that biopsy was carried out in only 10 cases. The ages of these 10 patients, 7 men and 3 women, ranged from 30 to 65 years (mean, 55 years). Six patients are alive 7 to 9 years (86 to 105 months) after their first examination. Four patients are dead; 2 died of coronary disease, 1 of typhoid fever, and 1 of pneumonia.

Diffuse Arteriolar Disease With Hypertension, Group 2. Patients of this group have a higher and more sustained hypertension than those of Group 1. They may complain of being more nervous than

* These data were obtained by 1, subsequent visit and examination; 2, letter from patient or near relative; 3, letter from patient's home physician, and 4, statement from the State Bureau of Statistics in case of death, in certain instances.

† We prefer this term to that of essential hypertension because it stresses the importance of dynamic or organic changes in the arterioles. There are always, however, coexisting changes of varying degree in the arteries.

formerly, but their general health is good and their cardiac and renal functions are satisfactory. The changes in the retinal vessels are more marked than in Group 1, but retinitis is not present. Correspondingly, the arterioles of muscles are shown to have changes more frequently. In a study of these patients, the impression is obtained that the disease is more progressive than in cases belonging to Group 1. In our group of 26 cases, 14 men and 12 women, aged 21 to 59 years (mean, 41 years) data revealed that 9 patients were alive 6 to 9 years (74 to 107 months) later, and 17 were dead. It is of interest that one of the living patients was examined for the first time 10 years before biopsy was carried out in 1920 and, at that time, the systolic blood pressure was 210 mm. of mercury and the diastolic, 120. Thus, it appears that certain patients belonging to this group may live comfortably for many years.

Diffuse Arteriolar Disease With Hypertension, Group 3. In this group, the hypertension is often high and sustained. On palpation, diffuse changes in the arteries usually can be demonstrated such as thickened, rubber-like radial, brachial, superficial temporal, posterior tibial, and dorsalis pedis arteries. Although cardiac and renal functions may be adequate, sometimes there are minor alterations in function as indicated by dyspnea on exertion, characteristic changes in the electrocardiogram and nocturia. Nervousness, headache, and vertigo are often annoying symptoms and visual disturbances may occur. Albuminuria and microscopic hematuria may be present. An important criterion is the presence of angiospastic retinitis,[18] together with definite sclerotic changes in the arterioles, but edema of the disks is not present. Changes in the arterioles of muscles are more numerous and more marked than among patients belonging to Group 1.

It is of great interest that, even in cases of Group 3, there may be a remission in the activity of the pathologic process. The patient feels better and stronger and headaches or vertigo may disappear. There is evidence in the retina of previously active retinitis and many small arterioles may become obliterated. In 1 such case, a number of small arterioles of the retina had undergone thrombosis and, on biopsy, the same process was seen to have taken place in some arterioles of the skeletal muscle. It is a question whether or not cessation of arteriolar spasm could be responsible for the remission.

In 37 cases of this group, 22 men and 15 women, the ages were 22 to 57 years (mean, 42 years). The prognosis was serious, because 79 to 90 months after examination, 34 patients were dead and only 3 were living. One of the latter is well, however, 7 years after biopsy of the muscle was made and the blood pressure has been as low as 130 mm. of mercury systolic and 90, diastolic.

Diffuse Arteriolar Disease With Hypertension, Group 4. All observers are agreed that patients belonging to this group are in a very serious condition. This fact is emphasized further by our

follow-up study which indicated that the great majority of the patients died within 1 year. The characteristic symptoms are nervousness, asthenia, loss of weight, headache, visual disturbances, dyspnea on exertion, and nocturia. Also, there may be obvious neurologic lesions. The objective findings are a persistently elevated blood pressure, palpable diffuse arterial thickening of the peripheral arteries, and retinal changes. The important retinal alteration is edema of the disks. There is also marked spastic and organic narrowing of the arterioles with diffuse retinitis. Albuminuria, cylindruria, and erythrocytes are usually present. Cardiac and renal functions may be adequate but, sooner or later, they become impaired. Associated with the terminal picture, there may be failure of the functions of the brain, heart, and kidney simultaneously. This fact suggests widespread anoxemia owing to decreasing arteriolar blood supply. The arterioles of muscle of 65 patients were examined by biopsy. As was to be expected, the abnormal findings were more frequent and more marked than in any of the other groups but, in a few cases, they were slight or absent. The ages in this series of 146 cases, 99 males and 47 females, were 8 to 64 years (mean, 40 years). The prognosis was very serious; 79% of the patients were dead within a year. However, among a few patients, the course is not so rapid. Some patients even have periods of subsidence of the retinitis accompanied by clinical symptoms which suggest remission. One of our patients is alive, 11 years after her first visit. Similar cases belonging to Group 3 were considered previously. Thus, in Group 4 also, spasm of the arterioles[18] may determine whether the condition is progressive. Such subsidence of severe retinitis was noted by Liebreich[11] who gave the first detailed description of the ophthalmoscopic findings in cases of albuminuric retinitis in 1859. Fishberg and Oppenheimer,[4] in 1930, reported in a case of malignant hypertension the healing of severe retinitis with no recurrence over a period of 4½ years. We reported a similar case in 1929 and, since that date, have seen 4 additional cases. We have observed a few cases of Group 4 in which the course was very rapid. The significant symptoms were sudden severe headaches, gross hematuria, and pains in muscles, accompanied by a persistently high blood pressure, marked narrowing of the retinal arterioles without apparent sclerosis and absence of distinct changes in the arterioles of muscles. A progressive, angiospastic mechanism seems to offer the best explanation.[18] Evidence is also accumulating that, even when there is marked pathologic change in the arterioles, as in some cases of Group 4, compensatory mechanisms, at present obscure, still may permit periods of improved metabolism in tissues and a reasonably comfortable existence.

To distinguish clinically between the four groups usually is not difficult. Some patients may have to be observed over several

months to determine whether they belong to Group 1 or 2. A given case may be markedly progressive so that although at first examination it appears to belong to Group 1 or 2, it may rapidly assume the characteristics of Group 4. On the other hand, there are cases in which there is little progression over a period of many years; a majority of these belong to Group 1, but a moderate number to Group 2 and a few to Group 3. Because the arterioles throughout the organs of the body seem to be the chief point of attack and can be visualized readily only in the retina, the findings obtained on ophthalmoscopic examination are very important. Patients who have only mild narrowing (increased tonus) or sclerosis of the retinal arterioles usually will fall into Group 1. Patients usually are placed in Group 2 if they have moderate to marked sclerosis of the retinal arterioles, whether of the chronic type, characterized especially by exaggeration of the arterial reflex and arteriovenous compression, or of the postangiospastic type characterized especially by generalized and localized irregular narrowing of the arterioles. Thrombosis of retinal veins or retinitis of the arteriosclerotic type may occur among patients of this group.

Patients who have retinitis of the angiospastic type, characterized especially by edema, cotton-wool patches, and hemorrhages in the retina superimposed on a combination of sclerotic and spastic lesions in the arterioles, belong to Group 3. If measurable edema of the disks is added to this picture the case belongs to Group 4. Diffuse retinitis and edema of the disks may develop in association with active spastic narrowing of the arterioles in certain cases of hypertensive disease of acute onset.[17] This type of retinitis may subside at times without the development of additional anatomic changes in the arterioles which characterize the typical case of Group 4.

Histologic Study of Arterioles of Muscles. The histopathologic study of the arterioles in small portions of the pectoralis major muscle obtained by biopsy in this series of cases has confirmed the previous work of Kernohan, Anderson, and Keith[8–10] that organic changes in such vessels do occur in cases of hypertensive disease. As previously noted and confirmed by Moritz and Oldt,[12] the most consistent change was an increase in the thickness of the arteriolar wall. The ratio of the diameter of the lumen to the thickness of the wall was found to be decreased. Following the plan of Kernohan, Anderson, and Keith,[10] in each biopsy at least four representative arterioles cut in cross-section were measured, four measurements being taken of the wall and two of the lumen. The mean of these measurements then was computed and a ratio was obtained by dividing the mean diameter of the lumen by the mean thickness of the wall. The mean of the ratios of the four or more representative arterioles obtained by measuring each specimen, gives a figure which has been used for each case. The mean ratio in the normal arteriole is 2.0 (1.7–3.0).

In addition to quantitative changes in the walls of the arterioles, we have observed certain other changes from the normal which we have termed qualitative. These include an increase in the number and size of the nuclei in the arteriolar muscle in association with and more or less commensurate with the decrease of the ratio. Also, we have observed an increase in the number and size of the nuclei in the intima of the arteriole, organized thrombosis, and evidence of arteritis and periarteritis as indicated by the presence of lymphocytes and fibroblasts in the media and adventitia. Also, in some cases, usually those whose ratios of lumen-to-wall were reduced definitely, arterioles have been found in which the lumen was completely closed without the presence of thrombosis. In no instances have we observed necrosis or degenerative changes in the arterioles, such as have been described as existing in vessels of the kidney of comparable size. It has been suggested that the reduced ratio of lumen-to-wall might be entirely the result of arteriolar spasm which was so persistent that it did not relax even after removal of the tissue from the body. The work of Moritz and Oldt has shown that this change can be reproduced neither by variations in histologic technique nor by vasoconstricting drugs in animals. The qualitative changes seen in the arterioles are further evidence that the changes are organic and that diffuse organic arteriolar injury may take place in cases of hypertension.

A careful analysis of the data obtained from the examination of the arterioles of muscles of 138 of the cases represented in this paper has shown that the changes are not consistent and that there is not a definite correlation between the findings in the arterioles of muscles and the division of cases into the four groups, the clinical severity of the disease, the length of life of the patient after the biopsy was taken, or the changes in the retinal arterioles. For example, there are some patients of Group 4 who died within a few months and had marked changes in the retinal arterioles but who had very few changes in the arterioles of muscles. Also, there are some patients in Groups 1 and 2 who are still living after more than 5 years and who had minimal changes in the retinal arterioles but who exhibited rather marked reduction of the ratio of lumen to wall and, also, definite qualitative changes in the arterioles of their muscles. However, when all the data are analyzed, it is found that, in general, a greater percentage of patients who have marked changes in the arterioles of muscles belong to Group 4 (Tables 2 and 3), have corresponding changes in the retinal arterioles and have a more serious prognosis. Thus, of 9 patients who had sclerosis of the retinal arterioles, Grade 0 to slight, only 25% had a ratio of lumen-to-wall of the arterioles of muscles of less than 1.4, although, in 81 cases of sclerosis of the retinal arterioles, Grade 1 to 2, 70% had a ratio of less than 1.4, and, of 48 cases of sclerosis of the retinal arterioles, Grade 3 to 4, 86% had a ratio of less than 1.4. Again,

of 34 patients with mean ratios of lumen-to-wall greater than 1.3 of the arterioles of muscles, 50% were dead in 2 years, although of 98 cases, in which the mean ratios of lumen-to-wall were 1 to 1.3, 70% were dead in 2 years and, of 6 patients who had ratios less than 1, all were dead in 2 years.

TABLE 2.—RATIOS OF LUMEN-TO-WALL, ARTERIOLES OF MUSCLE.

Hypertension, group.	Total patients.	Ratio of lumen-to-wall.		
		Maximum.	Minimum.	Mean.
1	10	1.8	1.3	1.7
2	26	1.9	0.8	1.3
3	37	2.0	1.0	1.3
4	65	1.8	0.9	1.2

TABLE 3.—QUALITATIVE CHANGES IN ARTERIOLES OF MUSCLE.

Hypertension, group.	Total patients.	Definite proliferation of intima, patients.	Patients.		Any qualitative changes present.	
			Organized thrombosis.	Arteritis, periarteritis.	Total patients.	Per cent of total patients.
1	10	1	0	0	1	10
2	26	11	1	2	11*	42
3	37	6	4	1	10*	28
4	65	22	9	3	31*	48

* In some cases, more than one type of change was found.

Prognosis. The outlook for patients who have essential hypertension affords a striking example of the variableness of processes of the disease. The present series of cases offers a good control for

TABLE 4.—PATIENTS ALIVE 5 TO 9 YEARS AFTER FIRST EXAMINATION.

Hypertension, group.	Total patients.	Patients alive.		
		Male.	Female.	Total.
1	10	4	2	6
2	26	4	5	9
3	37	2	1	3
4	146	0	1	1*
Total	219	10	9	19

* This patient was alive 11 years after first examination.

TABLE 5.—PATIENTS DEAD 5 TO 9 YEARS AFTER FIRST EXAMINATION.

Hypertension, group.	Total patients.	Patients dead.		
		Men.	Women.	Total.
1	10	3	1	4
2	26	10	7	17
3	37	20	14	34
4	146	99	46	145
Total	219	132	68	200

any specific form of therapy as treatment consisted of general measures, especially with regard to diet and rest and the regular use of certain sedatives. If the fact is considered that only 19 patients, or 9% of our entire series of 219, were alive 5 to 9 years after the

diagnosis was made, the seriousness of the prognosis for all patients seems obvious. But, on further analysis, this grave outlook is more apparent than real, as a disproportionate number of the cases belonged in Group 4. There are some patients in each group and as many as 35 to 60% in Groups 2 and 1 that are alive for a similar period of 5 to 9 years. These facts emphasize the significance of the original grouping particularly from the prognostic standpoint and also demonstrate that there are two predominating types of essential hypertension, the relatively stationary or benign and the rapidly progressive or malignant (Tables 4 and 5).

TABLE 6.—DEATH AT YEARLY INTERVALS AFTER FIRST EXAMINATION.

Years.	Per cent.			
	Group 1.	Group 2.	Group 3.	Group 4.
1	10	12	35	79
2	20	23	67	88
3	30	38	78	94
4	30	42	78	98
5	30	46	80	99

TABLE 7.—DURATION OF LIFE AFTER FIRST EXAMINATION.

Group.	Total patients.	Duration of life, months.	
		Median.*	Mean.†
1	10	100.0	
2	26	63.0	
3	37	15.9	27.6
4	146	5.4	10.5

* The time in months after first examination during which 50% of the patients in the group have died.

† The mean duration of life after first examination. Can be calculated only for the groups, practically all the patients of which have died; that is, Group 3 and Group 4.

The prognosis for cases of Group 3 and, especially, for cases of Group 4 is very serious. Because many more males than females belong to these two groups, the death rate is much higher among males than among females. A death rate, within 1 year, of 35%, in cases of Group 3, and 79%, in cases belonging to Group 4, is in distinct contrast with that of 10 to 12% in Groups 1 and 2. The mortality rate in cases of Group 4 approaches that found in certain forms of cancer (Table 6). In order to emphasize the difference in prognosis of the individual groups, survival curves as employed by statisticians were drawn* (Table 7; Fig. 1). The resulting curves are distinct for each of the four groups. As might be expected, there is a gradual increase in the steepness of the curves from that of Group 1 to that of Group 4. These statistical findings give further support to the conception that there are different types of essential hypertension.

* The authors are indebted to our statistician, Dr. J. Berkson, for making the necessary calculations for this table and chart.

Comment. In the present attempt to group cases of essential hypertension clinically, we realize that not all cases fall into one of the four groups mentioned. There are many patients who have this condition who have, in addition to arteriolar dysfunction, diffuse arteriosclerosis, more especially of the aorta and of the coronary and cerebral arteries. Atherosclerosis of these arteries may be the determining factor as to the course and prognosis. With more knowledge relative to the occurrence of atherosclerosis in such vital internal arteries and with the aid of more accurate diagnostic methods, these cases might be grouped in a much more satisfactory manner than is possible at present.

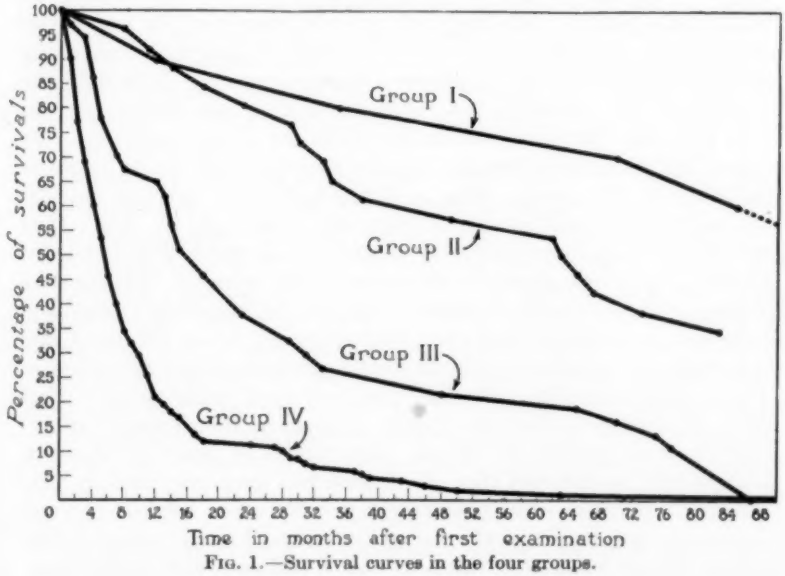

FIG. 1.—Survival curves in the four groups.

All students of the problem of essential hypertension are agreed that arteriolar dysfunction plays an important rôle in perpetuating the condition. Because the arterioles are small and are difficult to visualize in the peripheral organs, for example in the skin, mucous membranes, and voluntary muscle, the retina, as seen through the ophthalmoscope, offers a unique opportunity for observing these small vessels clinically from time to time. Therefore, we think that certain visible changes of the retinal arterioles have been of exceptional value in affording a clearer clinical conception of altered arteriolar function throughout the body. In the present grouping, the retinal observations occupy an important place. Technical difficulties still prevent satisfactory optical examination of arterioles in other living human tissues but, as these are gradually eliminated

in the human being, as they have been by Clark and his coworkers[2] in their study of the vessels in the rabbit's ear, it will be most interesting to compare findings obtained in such a manner with those in the retina. Our histologic study of the arterioles in muscle was an attempt to obtain somewhat similar information, particularly as to the presence or absence of pathologic change. Functional changes, of course, could not be estimated by such a technique.

We are fully cognizant of the limitations of the study of arterioles in muscle obtained by biopsy, in supplying important clinical data concerning the patient. Naturally, biopsy of muscle permits study of only a small sample of the general arteriolar bed of the body. There is also a certain personal equation in the examination of biopsy specimens. The biopsied muscles, however, in our series of cases were all examined by one of us who did not know anything about the type of hypertensive disease present. Although the changes in the arterioles are never great, they are definite to one who has had some experience in examining these specimens. In many instances, the changes in the arterioles are quite uniform throughout. In others, there is a great deal of variation, normal and markedly constricted arterioles being seen side by side. It is our opinion that definite organic changes in the arterioles of striated muscle usually are found in the more severe cases of hypertensive disease. Their absence, in some cases, and their extreme variability, in others, is evidence that they are secondary or, at the most, are concomitant changes as compared with generalized arteriolar spasm which most probably is the chief mechanism of hypertension. Possibly, the failure to find the organic changes in some cases of otherwise severe hypertensive disease, particularly in those of Group 4, is explained by the fact that the disease has been very rapidly progressive. Because similar, although usually more marked changes frequently are found in the arterioles of the kidney, choroid, and retina, it is probable that the arterioles in different parts of the body may be affected by organic change fairly uniformly in some cases although, in others, organic involvement may be very patchy. This is an argument in favor of the concept that vascular tissue, in some cases, may have a variable vulnerability in different organs and tissues.

It is quite evident that an important problem among these patients is the variation in the clinical course, length of life, and the pathologic lesions. Janeway[6] emphasized this point in his series of cases in 1913. This variation must be due to several factors. The apparent ones are the inherent condition of the elements composing the arterial and arteriolar wall, alteration of the nervous stimuli to arteries and arterioles, and the adaptability of the cardiovascular system as a whole. The various components of the latter obviously are exposed to abnormal stimuli and to excessive strain. It is still

not clear why, in some cases, the function of a single vital organ fails before others, or why, in some, several important organs cease to function simultaneously.

Goldblatt and his co-workers'[5] experimental production of chronic hypertension by curtailing the arterial blood supply to the kidneys naturally has revived the conception of both Volhard[16] and Fahr[3b] that essential hypertension is primarily attributable to renal dysfunction. There are many cases, however, that cannot be explained satisfactorily on such a hypothesis, as, for example, those cases associated with tumors of the adrenal and pituitary glands. It seems more logical to assume that there are several causes of hypertension, and as these factors become more clearly defined, clinical cases will be classified on an etiologic basis. In the meantime, accurate studies of the physiologic status and clinical course of the individual patient will lead to better grouping of the cases and, therefore, to a more accurate approach to the therapeutic problem of hypertension.

Summary. A study of 200 cases of essential hypertension revealed a constant abnormal factor; namely, excessive narrowing of the arterioles whether it be due to histologic change or increased vasoconstriction. The findings of previous investigators that there is a marked variation in the clinical course, length of life and pathologic lesions have been confirmed. The clinical subdivision of our cases into four groups has permitted an intelligent appraisal of the individual patient and has increased considerably the accuracy of prognosis. Furthermore, the statistical finding of a distinct survival curve for each of the groups adds support to the viewpoint that distinct types of essential hypertension can be differentiated clinically.

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THE POSTMORTEM WEIGHT OF THE "NORMAL" HUMAN SPLEEN AT DIFFERENT AGES.

By E. B. Krumbhaar, M.D.,
and
S. W. Lippincott, M.D.,
Philadelphia, Pa.
(From the Department of Pathology, School of Medicine, University of Pennsylvania.)

In connection with a study* of the ageing process in lymphatic tissue, it became desirable to have figures for the weight of the human spleen and its content of lymphatic tissue at different ages—data based on a larger material and extending over a greater period of the life span than are now available. This and a paper recently published[3] are the result of these studies.

The human spleen has notoriously the widest range of so-called "normal" weight of any of the important viscera, so that the frequently accepted "normals" of 150 to 200 gm. mean even less here than they do for other organs.

As might be expected, considerable differences may be found in the literature, ranging from Neugarten's[7] (1921) average normal of 115 gm. to Hyrtl's[4] (1846) 250 to 300 gm. Vierordt[10] (1893) tabulates 298 male and 305 female spleen weights divided into 36 groups between birth and 25 years. The weights given by him (combined for both sexes) rise from 10.7 gm. at birth to a maximum of 168.3 gm. at 25 years, the most marked rise occurring about the age of 15, with the males' spleens (after the first 2 years) weighing slightly more than the females'.

Lubarsch[5] (1926) has tabulated spleen weights for both sexes in 11 groups between birth and 40 years. There were 484 females and 541 males (total, 1025), selected from the Charité Hospital on the basis that the spleen showed no noteworthy structural changes. Starting at 9.5 gm. as the spleen weight at birth for both sexes, the weights increased, with no significant differences between sexes, to 77 gm. for the 10 to 15 age group, 121 gm. at 15 to 20, 144 gm. at 20 to 30, and 144 gm. for 30 to 40. He regards 150 gm. as an average postmortem weight for the normal adult spleen. In 569 males and 233 females (total, 802), selected on the same basis by Rössle and Roulet[9] (1932), somewhat similar figures were obtained. Starting with the weights of 11.2 and 10.2 gm. at birth, the weights rose steadily to a maximum for males of 169.1 gm. in the third decade and for females of 153.7 in the fourth decade. From then on, their spleen weights decreased with increasing age, averaging near 112 gm. in the seventh decade, and near 103 gm. for all persons

* Chapter on Lymphatic Tissue in "Problems of Ageing" edited by E. V. Cowdry, Baltimore, Williams & Wilkins, 1939.

over 70. Two spleens over 90 years of age averaged 65 gm. Though the authors state that they found no constant or decisive ("durchgehenden") difference between the sexes, their figures show greater weights for the male, as high as 25%, in all but 6 of the 30 age groups studied. Neugarten (1921), on the other hand, found an average weight for males in the 25 to 40 age group of 113.3 gm. as compared to 140 gm. for females. However, Moon[6] (1928) and Ahronheim[1] (1937), like ourselves, found slightly but consistently smaller figures for the female than the male spleens. Pearl and Bacon[8] (1921–1924) found that the spleen increased in weight up to the 35-year period, after which it progressively declined. They computed from Oppenheimer's (1889) accidental deaths, that at 25 years the male spleen averaged 164.8 gm., the female 160.7 gm. In Moon's (1928) 2000 cases above 18 years of age, from the Philadelphia General Hospital before 1928, the spleen weight decreased progressively in each of the 8 decades studied.

Even Lubarsch's material is none too large when scattered over 11 age groups and his figures stop at the fortieth year, just when the changes of older life should be most intensively sought after. Rössle and Roulet's figures also do not cover the older age periods in desirable amplitude, and in neither was there any analysis of the types of disease met in the different age groups.

Method. Necessarily limited to postmortem material, we have collected our data in two main groups: 1, From persons dying from miscellaneous diseases; 2, from persons dying violent deaths. The first half of the study was based on the records in this department from autopsies made at the University Hospital and at the Philadelphia General Hospital after 1928. Protocols including body weight, spleen weight, anatomic diagnoses and description of spleen were available. Most of the cases came from the general hospital where there is a large number of chronic cases (tuberculosis and others). Working back from those most recently completed, suitable cases were listed by color and sex in 18 semi-decades (from birth to 80 years and over in the last group) until 2000 cases were assembled.

Following the method adopted by Lubarsch, no spleens that had noteworthy lesions were included. This was a simple matter when such conditions as leukemia, Hodgkin's disease, malaria, typhoid, infarcts, amyloid spleen, splenic tuberculosis, and so on, were met. Difficulty was, however, encountered with the borderline lesions such as "acute splenic tumor," which varies from a considerable enlargement to an insignificant change appearing in many febrile deaths. It is well known that the spleen appears in the anatomic diagnosis at autopsy more frequently than any organ in the body and usually with such diagnoses as congestion, or cellular hyperplasia. These, then, if inconsiderable in degree, had to be included if such a study was to be made at all, though it was recognized that the

results could not be interpreted as "normal" spleen weights. Arbitrarily all spleens weighing over 300 gm. were discarded, except where, as was occasionally the case, a spleen above 300 gm. had been shown to be "normal" to gross and microscopic examination.

Body weights (accurate to less than 1 kilo) were also listed, so that the relative as well as the absolute weights of the spleen could be compared for the sexes and blacks and whites at different age periods. If one assumes that in a given age group normal individuals' spleen weights should bear approximately the same proportion to the body weight, it was thought possible that some of the deviations of the mean spleen weights at different periods could be explained in this way; *e. g.*, a high mean spleen weight in a given age group would be accounted for if there was a corresponding high body weight. It was hoped, also, that sufficient information could be obtained about the nationalities of the subjects to indicate whether they would show any trend in spleen weights, such as the relatively lighter weight of the negro's spleen; but it did not prove possible to obtain sufficient reliable figures on this point to permit satisfactory analysis.

The recorded chief cause of death and the condition of the spleen were listed and these were made the basis of an analysis (by S. W. L.) which, as far as we know, has not been previously attempted, in an effort to group these causes into categories in each of which the effect on the spleen was more or less similar. It was hoped that this also might elucidate irregularities found in the mean curve of spleen weights. Thus a peak in a given age group, whether or not affected by an irregularity in the mean body weight in the same group, might be partly explained, let us say, by an increased number of acute infectious deaths or other conditions increasing the weight of the spleen in that group, or similarly a depression in spleen weight attributable to, let us say, an abundance of wasting disease in a given group.

It was found desirable to construct 18 groups (Table 3), which, while having neither a purely etiologic nor morbid anatomic basis of classification, were devised to group together conditions resulting from inflammatory, circulatory, neoplastic processes and the like (with a few necessary subdivisions) that would be expected to have similar effects on spleen weight. Obviously an individual might have a combination of diseases of which one must be selected for listing. For instance, a patient with paralysis agitans and bronchopneumonia would be listed in the latter category, as it would more definitely affect the final spleen weight. As a further example, in the case of malignant disease complicated by bronchopneumonia, if the latter was thought to have had a predominant effect on the spleen, it would be the one listed.

The first group includes those cases where congenital lesions were thought to have the predominant effect on the spleen (representing

1.3%). Next, metabolic and endocrine disorders include mostly such conditions as malnutrition and marasmus in infants, and in the older group, diabetes mellitus, Graves' disease, and so on (totalling 3.2%). The blood diseases include only those of the so-called primary type (0.79%). Hemorrhage (3.7%) includes frank hemorrhage, such as occurs from an ulcer in a hollow viscus, in contrast to thrombosis and embolism (5%), which also includes cerebral hemorrhage. The arteriosclerosis group (6.3%) is self-evident. The acute respiratory infections (21.7%) are made up chiefly of the various pneumonias; while the acute gastro-intestinal diseases (3.7%) include such conditions as appendicitis and enteritis Acute cardiovascular diseases (1.9%) are obvious, while acute other conditions (5.7%) include septicemia and miscellaneous acute disorders. The large chronic respiratory group (9.1%) is made up mostly of fibrocaseous, ulcerative tuberculosis (including acute exacerbations). Close to it in importance are the chronic cardiovascular diseases (7.6%), mostly of luetic and rheumatic etiology. In the next group, are other chronic states not included elsewhere (3.3%). Non-infectious cardiovascular renal and liver diseases (5.7%) are exemplified by such conditions as nephrosclerosis and toxic liver necroses. Malignant tumors (12.9%) rank second in importance to acute respiratory disease. Nervous diseases (1.3%) include both acute and chronic organic lesions, central and peripheral. Finally, all cases not fitting in the above arbitrary divisions fall into the miscellaneous section (8%). (See Table 3 for age distribution.)

Recognizing the shortcomings of statistics based on disease deaths, we have succeeded in also obtaining data on another series of 2000 spleen and body weights in cases of death from all kinds of violence, especially of those cases dying shortly after the violence and uncomplicated by infection or known accompanying disease.* They have been divided into the same 18 age periods as in the disease group. As it appeared that analysis according to sex and color would not contribute anything beyond that made on the first group, it was not carried out for the violent deaths. It was hoped, at first, that the spleens of this series might be regarded as "supposedly normal"

* Our heartiest thanks are given to the Medical Examiners and Coroner's physicians of Boston, New York and Philadelphia, whose generous coöperation alone made this study possible. Dr. Leary in Boston had a P.W.A. staff of 4 working for 3 months transcribing details of over 1000 cases from his excellent records extending back to 1916. Dr. Helpern, of the Manhattan Medical Examiner's Office, was equally helpful with tissues and records of over 1000 cases, while Dr. Werne, at the Jamaica, L. I., office, was most generous with the records and slides under his control. Dr. Crane and the other Coroner's physicians of Philadelphia kindly gave us records and tissues over many months as the cases were autopsied, though records of previous cases here were not available. In all the autopsy rooms the organs were weighed on scales in good working order. These were accurate to 5 gm., though the important factor of loss of splenic blood after death and after excision of the organ at autopsy could not be accounted for. The body weights represent actual weighings (except in one morgue where they were estimated by one person, practised over many years, and probably represent an accuracy of within 4 or 5 kilos).

spleens, but it soon became evident that two factors tending to decrease the weight of the spleen—hemorrhage and shock—could not be excluded, both because of their frequency and because of inconstant recording of such features and inability to give quantitative estimates. As both these phenomena tend to cause blood to be squeezed from the splenic reservoir, it is obvious that the mean weights for this group should be somewhat below normal. It was found, however, that averages obtained with shock and hemorrhage cases excluded as far as possible were only a few grams higher for most age groups than when such cases were included. In fact, in a few age groups, the hemorrhage and shock spleens averaged even higher weights than the general mean for that group.

Another factor that may interfere with the normalcy of the spleen weight in violent deaths is the length of time occurring between the violence and death. Though all cases were excluded when the spleen was noted as in any way abnormal, and less than a dozen included where there was any evidence in the body of complicating sepsis or even a terminal infection, yet the survival period was frequently not given, some lived more than a day or even a week or longer. Thus of 731 cases in which the survival period was known, 81% died within 24 hours, and 11 persons lived for more than a week after the violence. We do not believe, however, that this disturbing factor has materially influenced the mean values presented.

Analysis of the causes of the 2000 violent deaths is hampered by the different criteria used by the various pathologists—some indicating the type of violence, others the anatomic results and still others, both. Nor is it important to our main purpose that these be minutely classified. However, in general, it may be said that fractured skull—the commonest cause of death—was noted in 492 cases, of which 121 were specified as due to an automobile accident and doubtless many others were due to the same cause. All other fractures were responsible for 146 cases. "Multiple injuries" caused 241 deaths, of which 191 were listed as due to automobile accidents. We estimate that the automobile was responsible for about 25% of the total. This percentage is less than the 39.3% in the Metropolitan Life Insurance Company's figures (Dublin and Lotka[2]), which we have selected as a good basis for comparison. There were 305 deaths from gunshot wounds, 15.2% (as compared with 2.5% of the Metropolitan), and 179 from cuts and stab wounds. Excepting carbon monoxide poisoning (78 cases) and acute alcoholism (listed as the primary cause in 45 cases), poisons accounted for 123 cases. These were of 16 kinds, the most numerous being a score of cyanide cases. There were 75 deaths listed as due to falls, 61 to asphyxia, 42 drowned, 28 hanged or strangled, 49 to ruptured viscera, 48 crushed, 22 burned, and 66 from miscellaneous causes.

The fact that the curve of "violent" spleen weights is significantly lower than the "disease" curve indicates that the material of the

two groups is truly different, and yet the remarkable parallelism found in the details of the two curves suggest that neither is far from the true normal.

Finally, as the "disease" cases of the first group tended, in our opinion, to have spleens slightly heavier than the true normal, and the "violent" cases of the second group slightly lighter than normal, it was thought that combination of the spleen weights in all 4000 cases would give a curve for the different age periods that should be nearer the true normal than either of the individual groups (Chart 1).

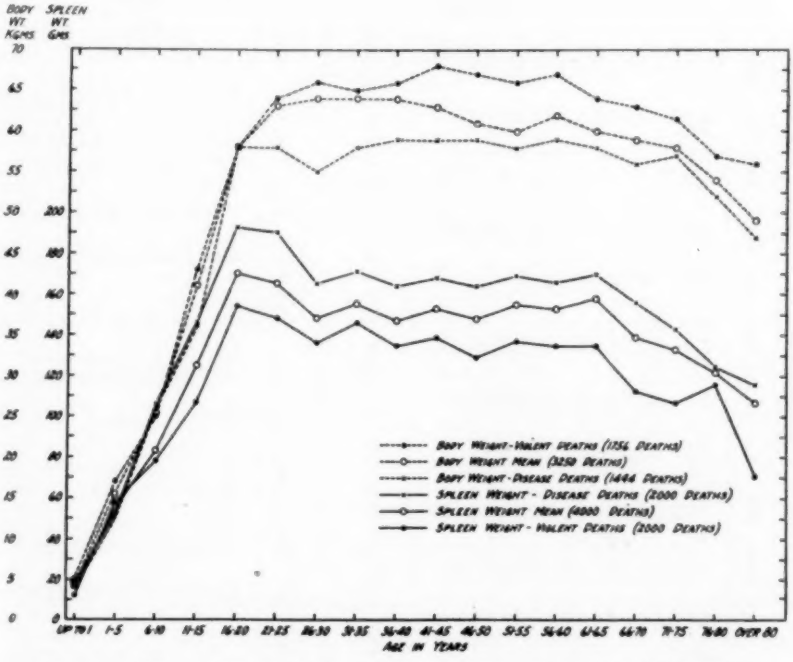

CHART 1.—Mean spleen and body weights at different age periods (4000 cases).

It is obvious, then, that this material, though similar in quality to that of other workers in the field, is far from ideal. Its value is limited by the many sources from which it is drawn, as well as by unknown or uncontrollable variables, and solace must be taken in the safety that exists in large numbers.

Results. The results of the "disease" group study (Tables 1 and 2; shown graphically in the uppermost and fourth curves of Chart 1) gave distinctly higher spleen and body weights in this series than in the German studies. Also the maximum weight was reached earlier in life. Statistical analysis showed that the 16 to 20 and 21 to 25 age groups had significantly heavier spleens than any

TABLE 1.—SPLEEN WEIGHTS AT DIFFERENT AGES (2000 "DISEASE" DEATHS).

Age (yrs.).	Male white.			Male black.			Female white.			Female black.			White.			Black.			Male.			Female.		
	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.
Up to 1	43	19.9	± 4.8	29	14.7	± 4.6	45	17.5	± 3.4	20	19.4	± 11.2	88	18.7	± 4.2	49	16.6	± 4.6	72	16.6	± 5.8	65	18.1	± 8.6
1–5	18	54	± 14.6	4	57.5	± 14.2	16	51	± 13.8	6	45	± 10.2	34	53	± 10.2	10	50	± 10	22	55	± 12.6	22	49	± 10.4
6–10	7	88	± 8.6	3	120	± 72	6	121	± 58	0	..	..	13	103	± 32	3	120	± 72	10	97.5	±36	6	121	± 58
11–15	18	140	± 36	2	80	± 28	14	173	± 60	3	95	± 8.2	32	155	± 34	5	89	± 14	20	134	± 34	17	159	± 50
16–20	23	247	± 44	13	161	± 46	19	166	± 30	18	172	± 46	42	211	± 30	31	167.5	±32	36	217	± 35	37	169	± 27
21–25	23	221	± 29	34	189	± 31	25	199	± 39	25	152	± 24	48	209	± 21	59	173	± 21	57	202	± 22	50	175	± 22
26–30	28	203	± 30	20	187	± 40	24	166	± 26	24	139	± 22	52	186	± 12.2	44	161	± 20	48	197	± 24	48	152	± 17
31–35	37	204	± 30	20	135	± 28	26	175	± 30	18	141	± 39	63	192	± 22	38	138	± 24	57	180	± 23	44	161	± 24
36–40	56	192	± 24	30	157	± 24	34	153	± 24	31	134	± 24	90	179	± 18.6	61	145	± 17.4	86	179	± 18.6	65	144	± 17.2
41–45	58	175	± 24	28	143	± 34	42	184	± 24	28	157	± 36	100	179	± 17.4	56	150	± 24	86	165	± 19.8	70	174	± 22
46–50	102	170	± 15.8	24	126	± 30	40	191	± 28	25	131	± 26	142	176	± 13.8	49	128	± 20	126	161	± 14.2	65	168	± 20
51–55	98	185	± 17.4	23	127	± 22	39	183	± 30	24	120	± 30	137	185	± 15	47	124	± 19.4	121	174	± 15.2	63	159	± 24
56–60	92	180	± 20	28	169	± 34	48	158	± 32	15	102	± 9.1	140	174	± 17.4	43	146	± 24	120	178	± 17.2	63	145	± 26
61–65	91	192	± 26	20	135	± 28	51	164	± 24	13	88	± 24	142	182	± 18.2	33	116	± 22	111	181	± 22	64	149	± 22
66–70	78	170	± 16	8	167	± 10	43	138	± 18	7	106	± 32	121	158	± 13.4	15	138	± 62	86	170	± 17.6	50	133	± 16.4
71–75	54	158	± 19.2	10	99	± 28	40	141	± 20	5	92	± 22	94	151	± 14.2	15	97	± 22	64	149	± 17.6	45	135	± 19
76–80	34	123	± 17	5	110	± 32	20	136	± 32	1	60	..	54	128	± 15.8	6	102	± 32	39	121	± 15.4	21	133	± 30
Over 80	30	127	± 24	2	115	± 64	10	95	± 42	2	70	± 14.2	40	119	± 20	4	93	± 40	32	126	± 22	12	91	± 18

TABLE 2.—BODY WEIGHTS AT DIFFERENT AGES ("DISEASE" DEATHS).

Age (yrs.).	Male white.			Male black.			Female white.			Female black.			White.			Black.			Male.			Female.		
	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.
Up to 1	35	4.8	±0.7	21	3.4	± 0.6	33	4	± 0.8	17	3.2	± 0.8	68	4.4	±0.3	38	3.3	± 0.1	56	4.3	±0.3	50	3.7	±0.2
1–5	11	11.5	±2.8	1	14	..	13	13.9	± 4	2	11	± 1.4	24	12.8	±2.6	3	12	± 1.8	12	11.7	±2.6	15	13.5	±3.6
6–10	3	24.3	±2.8	2	21.5	± 0.7	2	34	± 7	0	..	..	5	28.2	±5.4	2	21.5	± 0.7	5	23.2	±2.2	2	34	± 7
11–15	15	34.5	±7	0	..	..	9	39	± 9.8	1	43	..	24	36	± 5.2	1	43	..	15	34.5	±7	10	39.1	±8.8
16–20	13	55	± 6.2	1	22	..	8	53	± 4.6	5	78	± 9.2	21	54.5	±4.2	6	69	± 18.6	14	53	± 7.4	13	63	± 8.2
21–25	14	65	± 5.6	3	55	± 9.4	9	52	± 5.8	6	49	..	23	60	± 5	4	53	± 7.6	17	63	± 5.2	10	52	± 5.4
26–30	21	58	± 3.6	5	47	± 15.4	13	52	± 6	5	56	± 17.2	34	56	± 3.2	10	51	± 12	26	56	± 2.6	18	53	± 6.6
31–35	17	59	± 4	0	..	..	10	55	± 11.4	5	60	± 13	27	57	± 5	5	60	± 13	17	59	± 4	15	56.5	±8.4
36–40	27	61	± 6.4	6	62	± 7	16	53	± 6.4	8	64	± 13.4	43	58	± 4.8	14	63	± 8.2	33	61	± 5.4	24	56	± 6.4
41–45	48	57	± 3.4	26	58	± 4.4	33	57	± 4.2	27	64	± 6.4	81	57	± 2.6	53	61	± 4	74	57.5	±2.8	60	60	± 4
46–50	91	58	± 2.6	23	60	± 8.4	35	62	± 6.6	27	56	± 8	126	60	± 2.8	50	58	± 5.8	114	59	± 2.6	62	59	± 5.4
51–55	95	59	± 3	23	58	± 5.8	37	57	± 5.2	22	54	± 6.6	132	58	± 2.6	45	56	± 4.4	118	59	± 2.8	59	56	± 4
56–60	83	58	± 3.4	28	56	± 4.8	45	65	± 9.6	13	57	± 9.8	128	60	± 4	41	57	± 4.6	111	57	± 2.8	58	63	± 7.8
61–65	81	61	± 4.6	19	56	± 4	48	55	± 5.4	10	53	± 3.4	129	59	± 3.6	29	59	± 4.6	100	60	± 3.8	58	55	± 4.8
66–70	70	58	± 3.6	8	51	± 5.4	43	56	± 4.2	6	51	± 8.2	113	57	± 2.8	14	51	± 4.6	78	57	± 3.4	49	55	± 3.8
71–75	52	58	± 4.2	9	53	± 5	38	54	± 4.4	5	69	± 26	61	56	± 3.2	43	59	± 10.4	90	58	± 3.8	14	55	± 5
76–80	31	53	± 4	5	53	± 6	19	49	± 5.2	1	47	..	50	52	± 3.2	6	52	± 5.2	36	53	± 3.6	20	49	± 5
Over 80	29	50	± 3.8	1	36	..	9	41	± 7.6	2	44	± 15.6	38	47	± 3.6	3	41	± 11.4	30	49	± 4	11	41	± 6.8

other group. The lower spleen weight level of the 26 to 30 age group was maintained with but little change to the 65th year; application of the regression coefficient indicates that in this section the line is the equivalent of a horizontal one. The maintenance of the spleen

TABLE 3.—ANALYSIS OF 2000 "DISEASE" CASES AS TO CAUSE OF DEATH.

Age (yrs.).	Congenital.	Metabolic and endocrine.	Blood diseases.	Hemorrhage.	Thrombosis and embolism.	Arteriosclerosis.	Acute respiratory.	Acute cardiovascular.	Acute gastro-intestinal.	Acute other conditions.	Chronic respiratory.	Chronic cardiovascular.	Chronic other conditions.	Non-infectious cardiovascular renal and liver diseases.	Tumors.	Nervous.	Miscellaneous.	Total.
Up to 1 year																		
No. of cases	21	39	1	9	..	....	35	..	1	8	3	....	7	....	2	..	11	137
Per cent	15.5	28.5	0.7	6.6	..	....	25.6	..	0.7	5.8	2.2	....	5.1	....	1.5	..	8.0	6.85
1–5																		
No. of cases	2	....	..	..	1	....	12	2	6	6	4	1	4	....	1	2	3	44
Per cent	4.5	....	..	..	2.3	....	27.3	4.5	13.6	13.6	9.1	2.3	9.1	....	2.3	4.5	6.8	2.20
6–10																		
No. of cases	....	....	..	1	..	....	8	..	1	3	....	1	....	....	2	..	....	16
Per cent	....	....	..	6.2	..	....	50.0	..	6.2	15.8	....	6.2	....	....	12.5	..	....	0.80
11–15																		
No. of cases	....	....	1	2	..	....	2	1	1	3	2	4	4	4	4	3	6	37
Per cent	....	....	2.7	5.4	..	....	5.4	2.7	2.7	8.1	5.4	10.8	10.8	10.8	10.8	8.1	16.2	1.85
16–20																		
No. of cases	....	1	..	3	..	....	11	2	3	4	24	5	2	2	5	2	9	73
Per cent	....	1.4	..	4.1	..	....	15.0	2.7	4.1	5.5	32.0	6.8	2.7	2.7	6.8	2.7	12.3	3.65
21–25																		
No. of cases	....	1	1	1	..	....	21	1	3	9	43	2	1	4	4	1	15	107
Per cent	....	0.9	0.9	0.9	..	....	19.6	0.9	2.8	7.4	40.0	1.9	0.9	3.7	3.7	0.9	14.0	5.35
26–30																		
No. of cases	....	2	3	1	..	....	23	3	5	10	12	13	4	9	7	1	3	96
Per cent	....	2.1	3.2	1.0	..	....	24.0	3.2	5.2	10.4	12.5	13.5	4.2	9.4	7.3	1.0	3.2	4.80
31–35																		
No. of cases	....	2	..	5	..	....	20	5	5	7	15	15	2	6	9	..	10	101
Per cent	....	2.0	..	5.0	..	....	19.8	5.0	5.0	6.9	14.8	14.8	2.0	5.9	8.9	..	9.9	5.05
36–40																		
No. of cases	....	3	2	10	7	....	34	1	5	12	15	16	3	5	24	1	13	151
Per cent	....	2.0	1.3	6.6	4.1	....	22.5	0.7	3.3	7.9	9.0	10.6	2.0	3.3	15.9	0.7	8.6	7.55
41–45																		
No. of cases	....	1	..	12	9	1	37	4	9	7	12	18	10	12	11	4	8	155
Per cent	....	0.6	..	7.7	5.8	0.6	23.9	2.6	5.8	4.5	7.7	11.6	6.4	7.3	7.1	2.6	5.2	7.75
46–50																		
No. of cases	....	2	1	10	14	2	40	2	4	10	8	16	6	10	32	6	24	187
Per cent	....	1.1	0.5	5.3	7.5	1.1	21.4	1.1	2.1	5.3	4.3	8.5	3.2	5.3	17.1	3.2	12.8	9.35
51–55																		
No. of cases	....	2	1	11	17	5	37	4	7	5	12	20	4	12	45	..	7	189
Per cent	....	1.1	0.5	5.8	9.0	2.6	19.6	2.1	3.2	2.6	6.4	10.6	2.1	6.4	23.8	..	3.7	9.45
56–60																		
No. of cases	....	4	1	4	13	18	31	5	6	9	12	16	1	14	33	3	15	185
Per cent	....	2.2	0.5	2.2	7.0	9.7	11.8	2.7	3.2	4.9	6.5	8.6	0.5	7.6	17.8	1.6	8.1	9.25
61–65																		
No. of cases	....	2	2	3	14	21	36	1	6	6	7	11	2	7	40	..	17	175
Per cent	....	1.1	1.1	1.7	8.0	12.0	20.6	0.6	3.4	3.4	4.0	9.1	1.1	4.0	22.9	..	9.7	8.75
66–70																		
No. of cases	....	3	..	..	10	21	31	3	4	6	8	8	8	15	8	2	9	136
Per cent	....	2.2	..	..	7.3	15.5	22.8	2.2	2.0	4.4	5.9	5.9	5.9	11.0	5.9	1.5	6.6	6.80
71–75																		
No. of cases	....	....	..	1	8	31	22	..	4	2	2	4	3	6	20	..	4	107
Per cent	....	....	..	0.9	7.5	2.9	20.6	..	3.7	1.9	1.9	3.7	2.8	5.6	18.7	..	3.2	5.35
76–80																		
No. of cases	....	1	..	1	2	9	18	1	2	4	3	2	1	3	7	..	6	60
Per cent	....	1.7	..	1.7	3.3	45.0	30.0	1.7	3.3	6.7	5.0	3.3	1.7	5.0	11.7	..	10.0	3.00
Over 80																		
No. of cases	....	....	1	..	3	16	15	..	....	....	....	3	1	2	3	..	....	44
Per cent	....	....	2.3	..	6.8	36.3	34.1	..	....	....	....	6.8	2.3	4.5	6.8	..	....	2.20
Total																		
No. of cases	23	63	14	74	98	124	433	35	72	111	182	155	63	117	257	25	160	2000
Per cent	1.2	3.2	0.7	3.7	4.9	6.2	21.6	1.8	3.6	5.6	9.1	7.5	3.2	5.6	12.8	1.2	8.0	

weight up to 65 years, in spite of the tendency to increasing arteriosclerosis and fibrosis of the spleen, might be taken as indirect support for the hypothesis that has been advanced that there is an increase of lymphatic tissue in older middle life. This question is considered in more detail in our second paper in this study (*Am. Jour. Path*). After 65 years, there occurred a sharp and statistically significant loss of both spleen and body weight.

Analysis of the causes of death, though disappointing on the whole, did bring out a few points (Table 3). For instance, deaths from acute and chronic respiratory diseases were especially prevalent in the 16 to 20 and 21 to 25 age groups. It will be seen later, however, from a similar peak in the violent deaths in the 16 to 20 age group that the respiratory diseases could not be the only factors concerned in placing the heaviest spleen averages in these younger groups. As would be expected, arteriosclerosis became common in the older age groups. While it is obviously a factor to be dealt with in the terminal loss of spleen weight, presumably by damaging the circulation, its importance in the involution of old age cannot as yet be evaluated. The average spleen weight of our 247 tumor spleens between the ages of 16 and 70 was 154 gm., exactly the same as for all our "disease" spleens in those ages. This is in contrast to the tumor spleens in Moon's series, which were lighter than the general average. The 139 spleens of our chronic cardiovascular group averaged, as might be expected, considerably above (179 gm.) the general average for this period. Neither of these comparisons, however, throws any further light on age variations of the "disease" spleen curve.

Analysis of the nine subgroups of the classifications according to sex and color in the 18 age groups of the "disease" cases (Tables 1 and 2) shows that the number of whites and males predominated over that of blacks and females (71 and 59% respectively). In general, female spleens after puberty are lighter than male spleens, and in most groups significantly lighter; also, just as Moon had previously found, the spleens of negroes are significantly lighter than those of whites. (This interpretation is based on the facts that the sex and color differences could not be attributed to differences in mean body weights or to types of disease and on the finding that the differences of the means were more than twice the standard error; in other words, the chances are about 20 in 21 that mean weights from similar material would vary in a similar way.) Moreover, the spleens of whites and blacks show more of a difference than the spleens of males and females. Therefore, it would appear that sex was less of a factor than color. As might be expected, male whites had the heaviest spleens, and negresses the lightest; though the age groups in the negress class often did not have an adequate number of cases.

An analysis of the body weights of the disease group according to sex and color (Table 2) shows less difference among the 8 sub-

groups than do the spleen weights. The male whites were heavier than the blacks in 10 groups, and the males heavier than females in all but 2 groups after the age of 20, but the differences are too slight to be significant, except in a few cases. Unexpectedly, the female whites were heavier than the male blacks in 8 groups, the male blacks heavier in 7. It appears, then, that changes in the spleen weight curve at different age periods cannot be explained by fluctuations in the body weight curve or in their sex or color population. The averaged weight for all adult spleens (16 years or over) was 150.7 gm.; for spleens between the years of 16 and 70, 154 gm.; for all 4000 spleens, 140.7 gm.

Analysis of the histologic appearance of 868 spleens of the disease group (Table 4) shows that 75% were given diagnoses that should be accompanied by a tendency toward increased weight, even though such terms as "congestion" are variably used in routine descriptions and though the cases would not have been included by us if the changes had been marked. Only 2.5% were listed as atrophic. These histologic pictures, then, indicate that the splenic weights in this series of "disease" deaths tend on the whole to be above normal.

In the 2000 cases of violent deaths, analysis of mean spleen and body weights (Tables 5 and 6; 3d and 6th lines of Chart 1) shows that the heaviest spleen weights are attained in the same age group as in the disease groups, though a lower mean weight obtains throughout. The remarkable degree to which the spleen weight curves in the "disease" and the "violent" groups run parallel, has already been mentioned. In the "violent" group, also, where such extraneous factors as high incidence of respiratory or other disease, could not be operative, an early peak was followed by a more level curve, with a terminal drop. As this is more pronounced, however, in the "disease" curve than in the "violent" curve, which has more the appearance of a constant drop from the 16 to 20 age group, this point was investigated for significance statistically, with indecisive results as far as the "violent" curve was concerned. Analysis of the curve of the combined 4000 spleen weights (Table 5; 5th line in Chart 1) indicates clearly that there is a significantly high peak for the two age groups between 16 and 25, an essentially horizontal line for the spleen weights between 26 and 65 years and a significant loss of both spleen and body weight after 65 years.

At face value, these figures would indicate that the human spleen, after reaching a maximum weight soon after puberty, maintains a lower level until about the age of 65, when it again loses weight. If, however, one discounts the effect of the respiratory diseases in the 16 to 25 age groups and remembers the possibility that the "violent" curve may represent a gradual descent through adult life, instead of a hump and a plateau, then one cannot avoid the conclusion that ideal material might perhaps reveal a steady loss of spleen weight after puberty.

TABLE 4.—SPLENIC LESIONS OF CASES FROM TABLE 3.

Age (yrs.).	Congestion.	Infarction.	Atrophy.	Hyperplasia.	Chronic irritations.	Acute splenic tumor.	Miscellaneous.	"Normal."	Total.
Up to 1 yr.									
No. of cases	25	..	4	27	6	1	4	41	108
Per cent	23.1	..	3.7	24.9	5.6	0.9	3.7	37.0	12.45
1–5									
No. of cases	4	3	1	19	2	2	3	5	39
Per cent	10.3	7.7	2.6	8.8	5.1	5.1	7.7	12.8	4.49
6–10									
No. of cases	6	..	..	8	..	..	1	..	15
Per cent	40.0	..	..	53.3	..	..	6.7	..	1.72
11–15									
No. of cases	4	1	..	5	..	4	1	..	25
Per cent	56.0	4.0	..	20.0	..	16.0	4.0	..	2.88
16–20									
No. of cases	15	3	1	13	10	4	5	1	52
Per cent	28.8	5.8	1.9	25.0	19.2	7.7	9.6	1.9	5.99
21–25									
No. of cases	24	1	..	19	4	10	1	7	66
Per cent	36.4	1.5	..	28.8	6.1	15.1	1.5	10.6	7.60
26–30									
No. of cases	24	2	1	14	3	8	3	4	59
Per cent	40.7	3.4	1.7	23.7	5.1	13.6	5.1	6.8	6.79
31–35									
No. of cases	22	2	4	11	1	10	2	4	56
Per cent	39.3	3.6	7.1	19.7	1.8	17.9	3.6	7.1	6.45
36–40									
No. of cases	34	2	2	18	6	10	5	4	81
Per cent	43.2	2.5	2.5	22.2	7.4	12.3	6.2	4.9	9.32
41–45									
No. of cases	40	2	2	20	3	12	6	5	90
Per cent	44.0	2.2	2.2	22.2	3.3	13.3	6.7	5.1	10.36
46–50									
No. of cases	33	2	..	12	3	8	5	1	64
Per cent	51.6	3.1	..	18.8	4.7	12.5	7.8	1.6	7.37
51–55									
No. of cases	44	6	..	7	2	9	3	..	71
Per cent	62.0	5.5	..	9.9	2.8	12.7	4.2	..	8.17
56–60									
No. of cases	23	4	4	9	1	3	3	..	47
Per cent	49.0	8.5	8.5	19.2	2.1	6.4	6.4	..	5.41
61–65									
No. of cases	26	6	2	11	..	1	3	..	49
Per cent	53.1	12.3	4.1	22.4	..	2.1	6.1	..	5.61
66–70									
No. of cases	11	1	..	6	..	..	..	..	18
Per cent	61.1	5.6	..	33.3	..	..	..	..	2.07
71–75									
No. of cases	12	3	..	4	..	1	..	..	20
Per cent	60.0	15.0	..	20.0	..	5.0	..	..	2.30
76–80									
No. of cases	4	..	..	2	..	..	..	..	6
Per cent	66.7	..	..	33.3	..	..	..	..	0.69
Over 80									
No. of cases	1	..	1	..	..	..	..	..	2
Per cent	50.0	..	50.0	..	..	..	..	..	0.23
Total									
No. of cases	362	38	22	205	41	83	45	72	868
Per cent	41.7	4.4	2.5	23.6	4.7	9.6	5.2	8.3	

Study of the ratio of spleen weight to body weight in the 4000 cases (Table 6) shows that it is highest and significantly above subsequent ratios in the earliest age group (0.0042). From then on the slope of the ratio is slightly though not significantly down (from 0.0035 to 0.0022), except for a plateau in the groups between 51

TABLE 5.—SPLEEN WEIGHTS AT DIFFERENT AGES. (COMBINED "DISEASE" AND VIOLENT DEATHS.)

Age (yrs.).	2000 "disease" deaths.			2000 violent deaths.			Total, 4000.		
	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.
Up to 1 yr.	137	17.9	± 2.2	19	12	± 3.2	156	17	± 2.0
1– 5	44	52	± 8.2	71	58	± 4.4	115	55	± 4.4
6–10	16	106	± 30	73	78	± 7.2	89	83	± 8.2
11–15	37	146	± 30	57	107	± 12.4	94	125	± 14.4
16–20	73	192.5	± 23	111	154	± 12.2	184	170	± 12.0
21–25	107	190	± 16	163	148	± 8.6	270	165	± 7.6
26–30	96	165	± 5	214	136	± 9.2	310	148	± 7.6
31–35	101	171	± 17	191	146	± 9.8	292	155	± 8.8
36–40	151	164	± 13.2	209	135	± 9.2	360	147	± 7.8
41–45	156	168	± 14.4	175	139	± 9.8	331	153	± 8.6
46–50	191	164	± 11.8	164	129	± 9.2	355	148	± 7.8
51–55	184	169	± 12.8	142	137	± 10.6	326	155	± 8.8
56–60	183	166	± 14.6	142	135	± 10.4	325	153	± 9.6
61–65	175	170	± 16	102	135	± 13.4	277	158	± 11.4
66–70	136	156	± 13	89	113	± 12.4	225	139	± 9.6
71–75	109	143	± 13.8	43	107	± 11.6	152	133	± 10.2
76–80	60	125	± 14.8	24	116	± 17.4	84	122	± 11.6
Over 80	44	116	± 19.4	11	71	± 13.2	55	107	± 16.6

TABLE 6.—BODY WEIGHTS AT DIFFERENT AGES (COMBINED "DISEASE" AND VIOLENT DEATHS).

Age (yrs.).	2000 "disease" deaths.			2000 violent deaths.			Total, 4000.			Ratio of spleen weight to body weight.
	No.	Mean.	2SE.	No.	Mean.	2SE.	No.	Mean.	2SE.	
Up to 1 yr.	106	4	± 0.1	14	5	± 1.2	120	4.1	± 0.2	0.0042
1–5	27	12.7	± 2.2	51	17	± 1.2	78	15.5	± 1.2	.0035
6–10	7	26.3	± 4.4	48	25	± 2.0	55	25.2	± 1.8	.0033
11–15	25	36.4	± 5	48	43	± 3.6	73	41	± 3.0	.0030
16–20	27	58	± 5.8	58	103	± 2.0	130	58	± 2.0	.0029
21–25	27	58	± 4.4	148	64	± 2.2	175	63	± 2.0	.0026
26–30	44	55	± 3.8	200	66	± 1.8	244	64	± 1.8	.0023
31–35	32	58	± 4.6	180	65	± 1.6	212	64	± 1.4	.0024
36–40	57	59	± 4.2	194	66	± 2.0	251	64	± 1.8	.0023
41–45	134	59	± 2.4	141	68	± 2.8	276	63	± 1.8	.0024
46–50	176	59	± 2.6	149	67	± 2.0	325	61	± 1.8	.0024
51–55	177	58	± 2.2	118	66	± 2.6	295	60	± 2.8	.0026
56–60	169	59	± 3.2	125	67	± 2.2	294	62	± 2.2	.0025
61–65	158	58	± 3	88	64	± 2.6	246	60	± 2.2	.0026
66–70	127	56	± 2.6	77	63	± 4.4	204	59	± 2.0	.0024
71–75	104	57	± 3	40	61.5	± 4.4	144	58	± 2.6	.0023
76–80	56	52	± 3	21	57	± 6.2	77	54	± 2.8	.0023
Over 80	41	47	± 3.6	11	56	± 6.4	52	49	± 3.2	.0022

and 65 years (0.0026), where the ratio is significantly higher than those of age groups on either side. The ratio of spleen weight to body weight in all ages in the 4000 cases averaged 0.0027. Others have found similar results: the percentage of the spleen weight in the body weight having been found highest from 2 to 7 years (0.32 to 0.39%), falling to about 0.25% at 25 years.

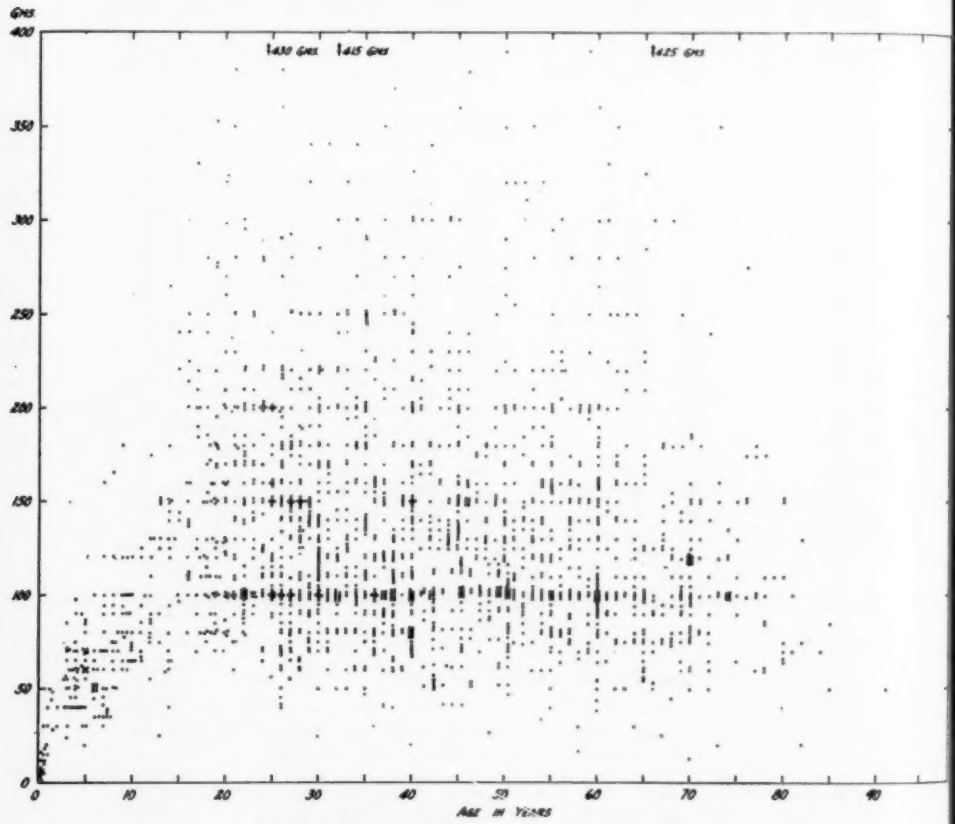

CHART 2.—Individual spleen weights at different ages (2000 violent deaths).

To illustrate the marked "scatter" of supposedly "normal" spleen weights, the individual spleen weights in the group of 2000 violent deaths have been charted (Chart 2). Recalling that these are from persons who from their history and postmortem examination gave no evidence of splenic disease, the deviation from the mean is unexpectedly great in all the age groups. Thus a male white, aged 45, weighing 135 pounds, who committed suicide with cyanide, had a spleen which at autopsy was reported as normal but weighed 400 gm.; a Jewess of 32, weighing 150 pounds, was

strangled—her "normal" spleen was found to weigh 415 gm. At the other extreme, an apparently normal Chinese of 40, weighing 124 pounds, was drowned and his spleen, reported "normal," weighed only 20 gm. Such examples are too numerous to be attributable to error or oversight of pathologic causes. While no explanation is forthcoming for this great variation, it is useful to know that adult spleen weights below 50 gm. or above 400 gm. do not necessarily indicate splenic disease. Weights of apparently normal spleens as low as 100 gm. and as high as 250 gm. are not at all uncommon. It must be emphasized, however, that the term "normal," especially when used by a number of observers, may be subject to considerable latitude of interpretation. Such elements of weakness, however, tend to be minimized by the large number of cases analyzed.

Summary. 1. Postmortem human spleen and body weights have been assembled in 18 age periods (semi-decades, with the last covering all cases over 80 years) in two main groups. In the first group, were studied 2000 cases dying from miscellaneous diseases but without noteworthy involvement of the spleen; in the second group, 2000 cases dying violent deaths.

2. In both of these groups, and therefore in the combined group of 4000 cases, the spleen reached a maximum average weight (170 gm. for the combined group) at the 16 to 20 year period. Between the ages of 26 and 65, the mean spleen weight remained approximately unchanged (155 to 160 gm. for the combined group). After 65 years, it fell markedly, until in very old spleens weights of less than 100 gm. were the rule.

The ratio of the spleen weight to body weight was found to be highest at birth and to fall steadily while the spleen was attaining its maximum absolute weight. From 26 years on, the ratio fell slightly, except for an apparent rise from 50 to 65 years.

3. In general, male spleens were heavier than female spleens and those of white people heavier than those of blacks. As the difference between spleen weights of whites and blacks was greater than that between males and females, sex appears to be a less important factor than color. In none of the above categories were mean spleen weight differences of individual groups to be attributed to corresponding differences in mean body weights.

4. The average weight for all our adult spleens (16 years or over) was 150.7 gm.; for spleens between the ages of 16 and 70, 154 gm.; for all 4000 spleens, 140.7 gm.

5. The weight of the apparently normal human spleen fluctuates within extremely wide limits. Weights as low as 100 gm. and as high as 250 gm. were not infrequently recorded, while even such weights as 50 and 400 gm. were occasionally given for what appeared to be normal spleens.

6. Analysis of the cause of death in the "disease" group showed little beyond the prevalence of acute respiratory disease in the cases

between 16 and 25 years of age and of arteriosclerosis in the older age groups. The former of these may well be a factor in the spleen weight peak in the two young groups, and the latter a factor in the loss of spleen weight in older life. Analysis of the histologic appearances in the "disease" group showed that about 75% of the spleens had diagnoses of lesions which should tend to cause an increase in weight, and only 2.5% were listed as atrophic.

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THE SIGNIFICANCE OF PERIPHERAL CIRCULATORY DISTURBANCES FOR THE DEVELOPMENT OF OSTEO-ARTHRITIS.

By David H. Kling, M.D.,

ASSISTANT PROFESSOR OF ORTHOPEDIC SURGERY, WHITE MEMORIAL HOSPITAL, LOS ANGELES, CALIF.

In 1909 Wollenberg[18] elaborated the theory that vascular deficiencies are a primary factor in the production of osteo-arthritis. He based this theory on the frequent occurrence of arteriosclerosis of the vessels of the bone marrow and synovial membrane in osteo-arthritis (hypertrophic arthritis). Experimentally, he produced overgrowth of the patella in dogs by circular ligature of the soft tissues. Pemberton[6] and his co-workers have repeated this experiment and supported Wollenberg's findings.

More recently Bernstein[2] pointed out that venous stasis may induce osteo-arthritis. After ligation of the popliteal veins in dogs he obtained degeneration of the articular cartilage of the knee joints, and after ligation of the lumbar vertebral veins he observed degeneration of the intervertebral disks, hypertrophy and osteophytes of the margins of the lumbar vertebræ.

On the other hand, the vascular theory was challenged by a number of authors. Pommer[15] observed that arteriosclerotic changes in osteo-arthritic joints are not more frequent than in normal joints of individuals past middle age. Walkhoff,[17] Axhausen and Pels[1] found that the changes of the patella after circular ligation are due either to minute injuries of the articular cartilage at the operation, or necrosis of the cartilage and bone, due to shutting off of the blood supply. The new bone formation is not due to osteophytes, as in osteo-arthritis, but to proliferation of fragments which are separated

from the patella by connective tissue. Axhausen advanced the theory that necrosis of articular cartilage induces the development of osteo-arthritis. Pommer regarded loss of elasticity of cartilage to be the initial lesion, which leads to reactive changes of the subchondral bone. Axhausen, Burkhardt,[4] Seeliger,[16] Haebler[7] and Key[9] produced osteo-arthritic changes in the joints of dogs, rabbits or guinea pigs by damaging the articular cartilage with physical and chemical means, such as cauterization or resection of small segments of articular cartilage or intra-articular injections of weak acid, alkali, or even normal saline solution.

TABLE 1.—RÉSUMÉ OF FINDINGS IN JOINTS OF LOWER EXTREMITIES AMPUTATED FOR GANGRENE DUE TO THROMBO-ANGIITIS OBLITERANS OR ARTERIOSCLEROSIS.

Case No.	Age.	Diagnosis.	Duration (yrs.)	Joints.	Remarks.
1	23	Thrombo-angiitis obliterans	4	Normal	Two amputations.
2	35	" "	..	Normal	
3	59	" "	10	Synovitis of ankle and knee joints. Inflammatory infiltration and thrombosis of synovial vessels. Erosions of the articular cartilages of the talus, tibia, femur and patella	Osteomyelitis second phalanx of large toe and tarsal bones.
4	64	Arteriosclerosis Mönckeberg type	..	Slight erosion of articular cartilage of femur and patella	
5	64	" " "	2	Obliteration and thickening of vessels in synovial membrane. Tarsal and ankle joints normal. Moderate erosion of articular cartilage of femur	Two amputations. Osteomyelitis of second phalanx, large toe. Died.
6	74	" " "	8 mo.	Normal	Gas infection.
7	56	" " "	2	Synovial membrane normal. Normal vessels prevail. Some show thickening and obliteration. Moderate erosion and osteophyte of ankle and knee joints	Two amputations. Osteomyelitis and suppuration of stump of large toe.
8	48	Arteriosclerosis with diabetes	12	Normal	Gangrene 6 wks. Osteomyelitis of large toe.
9	58	" " "	2	Erosion of cartilage of patella and femur. Hyperemia of infrapatellar fat pad	Two amputations.
10	59	" " "	12	Normal	Died.
11	59	" " "	7 mo.	Moderate hypertrophy of synovial membrane. Advanced osteoarthritis of knee joint	No history of joint complaint.
12	66	" " "	1	Synovial membrane normal. Slight erosion of patellar cartilage	Two amputations. Roentgen ray shows calcified vessels. Osteomyelitis of phalanx of large toe.
13	68	" " "	18	Normal synovial membrane. Erosion of articular cartilage of patella and femur	Two amputations.

The experimental evidence of these theories is subject to objections. Frequently, the methods employed were non-physiologic. Due to the small size of the joints of the animals, the action of the agent cannot be strictly localized. Finally, the changes may resemble, but are not identical with osteo-arthritis.

It occurred to me that the study of human joints in cases of severe, chronic organic diseases of peripheral blood-vessels would

give a more pertinent evaluation of the rôle of the vascular disturbances as a factor in the development of osteo-arthritis.

Material and Methods. The joints and blood-vessels of 13 lower extremities, which had been amputated because of gangrene due to arteriosclerosis or thrombo-angiitis obliterans, were studied

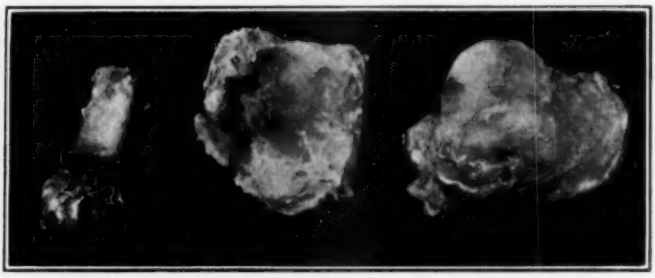

FIG. 1.—Thrombo-angiitis obliterans (Case 3). The metatarsus of the great toe, the articular surfaces of the tibia and talus show secondary osteomyelitis and suppuration, which has spread from the gangrenous area.

FIG. 2.—Thrombo-angiitis obliterans (Case 3). The articular surfaces of the first and second phalangeal joints of the large toe are intact. The patella and tibia show central erosions of the cartilage and thickening of the synovial membrane.

macroscopically and microscopically. Table 1 gives a summary of the findings. Thrombo-angiitis obliterans was present in 3 cases and arteriosclerosis was found in 10 cases. Of the latter group, 6 cases were complicated by diabetes mellitus. In 5 cases amputations had been performed at lower levels, such as toes or ankles, several months previously. Two cases (2 and 12) had bilateral amputations.

The patients who suffered from thrombo-angiitis obliterans were males between 23 and 59 years. In the arteriosclerotic group, there were 4 females and 6 males ranging in age between 48 and 74 years. The area of gangrene varied from the dorsum of one toe to extensive

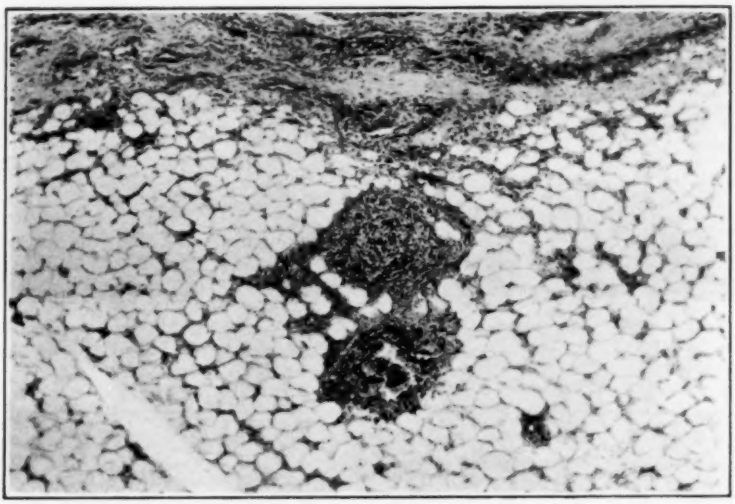

FIG. 3.—Thrombo-angiitis obliterans (Case 3). Section through the infrapatellar fat pad. Subacute synovitis with hypertrophy fibrosis and focal infiltration of the synovial membrane. Larger vessels are infiltrated and thickened but numerous newly formed small vessels are open. In the subsynovial fat, two large thrombosed and obliterated vessels are seen.

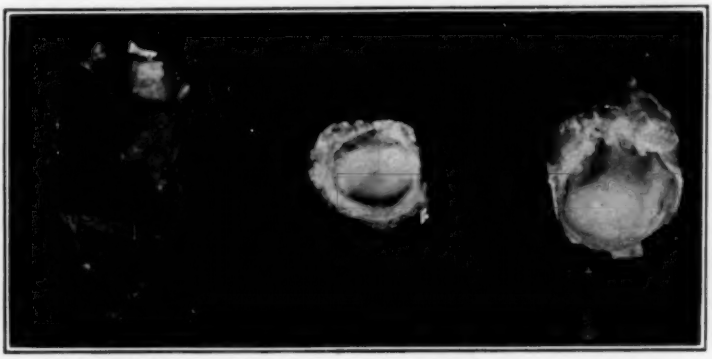

FIG. 4.—Thrombo-angiitis obliterans (Case 1). Gangrene of the left toe. The articular surfaces of the heads of the first and fifth metatarsals are intact. The surrounding joint capsules were normal.

necrosis of the foot and ankle. Osteomyelitis of the phalanges, tarsal bones or talus (Figs. 1, 7) was present in 4 cases. Only in 3 cases was the duration of clinical symptoms of circulatory disturbance less than 1 year. None of the patients gave a history of previous joint affections.

The Vessels of the Extremities. In all cases the femoral, tibial, peroneal, dorsalis pedis vessels and their small branches showed extensive and progressive lesions. In the cases of thrombo-angiitis

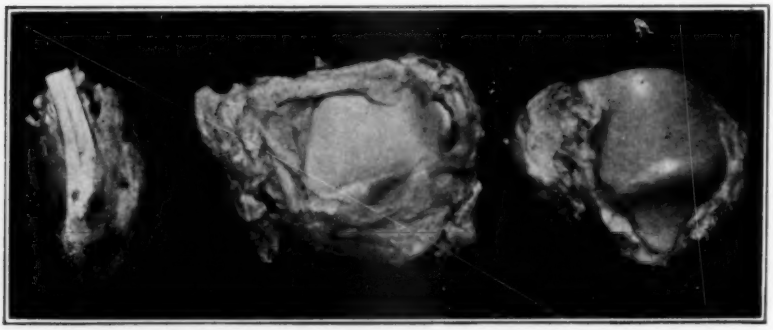

FIG. 5.—Thrombo-angiitis obliterans (Case 1). Section through the gangrenous toe. The plantar tendon intact. The articular surfaces of the talus and tibia and the synovial membrane are normal.

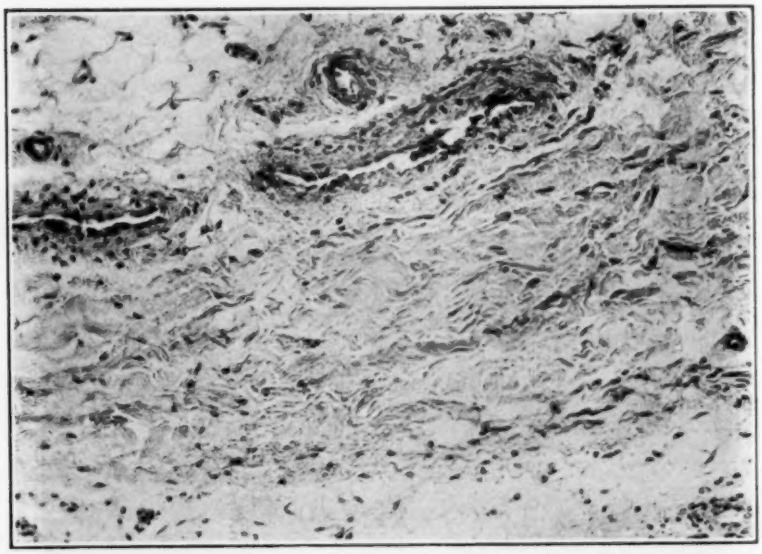

FIG. 6.—Thrombo-angiitis obliterans (Case 1). Normal synovial membrane of the lateral parts of capsule. Surface layer contains one to several rows of cells, subsynovial layer, partly areolar, fatty or fibrous. Smaller vessels normal, larger vessels somewhat thickened.

obliterans, more recent infiltration of the vessels and thrombosis was found, together with various stages of occlusion by fibrotic organization. In cases of arteriosclerosis, the vessels were narrowed or obliterated by thickening of the intima and media through

atheromatous and calcareous masses, by secondary inflammation and thrombosis and fibrotic organization. The sclerotic vessels were in some cases visualized in roentgenograms.

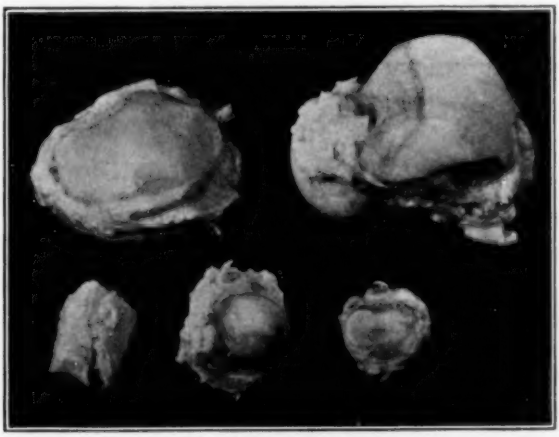

FIG. 7.—Arteriosclerosis, Mönckeberg type, (Case 5). Osteomyelitis of the first phalanx of the large toe. The articular surfaces of the metacarpus, the talus and patella are normal.

FIG. 8.—Arteriosclerosis, Mönckeberg type (Case 5). The articular cartilage of the knee joint shows fibrillation. In the central portion of the femur there is a deeper defect present.

The Synovial Membrane. In a case of thrombo-angiitis obliterans (Case 3), there was a subacute synovitis of the ankle and knee joints. The subsynovial tissue showed fibrosis and infiltration with round and plasma cells (Fig. 3). In 2 cases the synovial membrane was normal (Fig. 6). In 1 case of arteriosclerosis with advanced osteo-arthritis (Case 11), there was a moderate thickening of the

synovial membrane. In another case (Case 9), the infrapatellar fat pad was congested and showed hypertrophy. In 10 cases, the synovial membrane of the phalangeal, tarsal, ankle and knee joints appeared to be normal. In 4 cases, osteomyelitis spread, secondarily, to the phalangeal, tarsal and ankle joints.

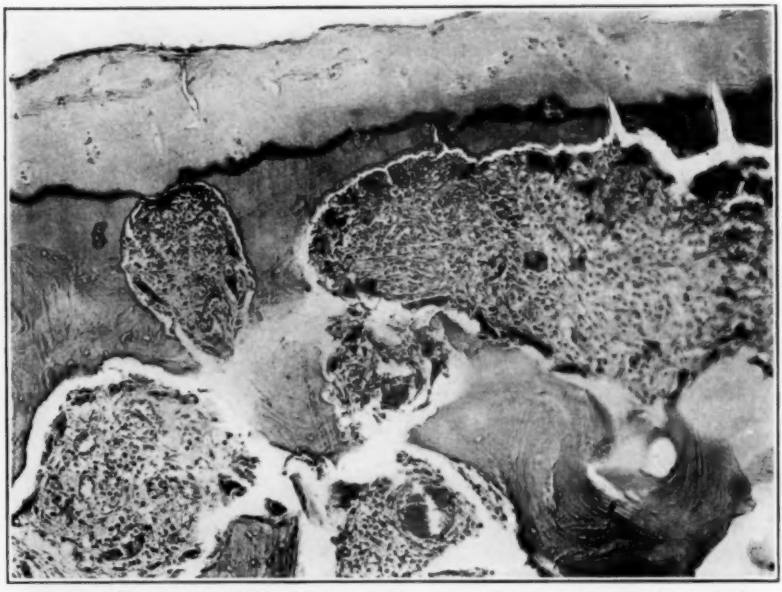

FIG. 9.—Thrombo-angiitis obliterans (Case 3). Section through the articular surfaces of the tibia showing incipient osteo-arthritis. The hyaline cartilage shows fibrillation and erosion. Smaller and larger clefts are seen in horizontal as well as vertical direction. In the deeper layers of the cartilage enlarged lacunæ with numerous cartilage cells are present. The irregular dark blue line of calcified cartilage and the subchondral bone plate are broken through in a number of places by cellular bone marrow, which contains giant-cell osteoclasts. A small and a large fragment of fractured necrotic bone lamellæ are seen in the middle and the right lower corner. The bone marrow is hyperemic and contains numerous newly formed vessels.

Synovial Vessels. In 1 of the 3 cases of thrombo-angiitis obliterans (Case 3), numerous vessels showed either inflammation and thrombosis or obliterating fibrosis, but others were found patent. Newly formed vessels were also present in the inflammatory areas (Fig. 3). In the arteriosclerotic group, marked changes in the synovial vessels were found in 2 cases (Cases 5 and 7). In all cases some vessels showed thickening of the intima and media, and even obliteration. Such changes, however, are found in normal joints in people past middle age. In a group with such advanced arteriosclerosis, it is remarkable to note the slight degree of change in the synovial vessels.

The Articular Cartilages. One case (Case 11), a woman aged 64 years, showed advanced osteo-arthritis of the knee joint. The

central portion of the cartilages of the femur, tibia and patella were eroded. The underlying bone showed eburnation, and osteophytes at the periphery. The patient, however, denied having any previous symptoms in this knee. In another case (Case 7, Fig. 8) there was erosion of the central portion of the articular cartilage of the patella, tibia and femur. Fibrillation of the cartilage was found in 6 knee and in 4 ankle joints. In 5 extremities, the joints were entirely normal. Even in the cases with lesions in the knee and ankle joints, the majority of the phalangeal and tarsal joints were intact (Figs. 2, 4, 5, 7). Bone changes varied from simple atrophy and decalcification to osteomyelitis with massive destruction and suppuration of the phalanges and tarsal bones (Figs. 1, 7). In such places, marked periostitis was present.

Under the areas of fibrillation or erosion of articular cartilage, reactive bone changes occur. These consist, first, of localized absorption of the subchondral compact bone and the calcified zone of cartilage by the invasion of cellular bone marrow, which contains mononuclear and giant cell osteoclasts (Fig. 9). Subsequently, osteoid tissue is laid down by a seam of osteoblasts and finally impregnated with lime salts. The proliferation of the new bone, which replaces the destroyed cartilage, may produce osteophytes. The cellular and fibrotic marrow is hyperemic and contains numerous newly formed vessels. In the fatty marrow the vessels were sparse but mostly normal.

Periarticular Tissues. The joint capsule, ligaments and tendons were normal, except in the immediate vicinity of gangrenous areas. Even in such instances, the involvement of tendons were often minimal (Fig. 5).

Discussion. From this study the following conclusions can be drawn:

1. In cases of advanced thrombo-angiitis obliterans, the synovial vessels may participate to a marked degree in the generalized inflammatory vascular lesions.

2. In severe arteriosclerosis with gangrene, the synovial vessels have been found only slightly or moderately involved. Various factors may contribute to the resistance of the synovial vessels against arteriosclerotic changes. First, the synovial membrane is supplied by a rich vascular network. The numerous anastomoses reduce the circulatory burden on any single blood-vessel. Secondly, Oberndorf[14] pointed out that the localization of arteriosclerosis is influenced by the amplitude of excursion of a blood-vessel, which is permitted by the surrounding tissue. Blood-vessels, which are located in osseous channels, such as the internal carotid artery, or are firmly bound to the surrounding tissues, such as the iliac, femoral, tibial and dorsalis pedis arteries, show the most advanced arteriosclerosis. The synovial vessels participate in the joint motions. This exerts a massaging effect which opposes the progress of

arteriosclerotic lesions. Venous congestion was not found in these synovial membranes, except in 1 case where the infra-patellar fat pad was hypertrophied and congested. These findings contradict the theory that vascular changes, especially arteriosclerosis, are a primary factor in the etiology of arthritis.

Lesions of the articular surfaces were not any more frequent than those found in a corresponding age group with normal extremities. All 10 patients with arteriosclerotic gangrene were over 40 years of age, only 2 (20%) of the cases showed a fully developed picture of osteo-arthritis. Numerous investigators have found some degeneration of articular cartilage and osteophytes in over 80% of people past middle age. Besides the slight degree of arteriosclerosis in the synovial vessels, other evidence confirms that these degenerative changes are not due primarily to vascular deficiency. The knee and ankle joints were usually more involved than the phalangeal and tarsal joints, while the greatest deficiency of circulation occurs in the distal part of the extremities. Secondly, the articular cartilage has an extremely low metabolic rate and very slight nutritional requirements (Bywaters).[5] Therefore, it is apt to be not greatly affected by deficiency of circulation. Finally, the initial lesions of osteo-arthritis consisting of fibrillation and erosion occur in the central portion of articular cartilage which is devoid of blood-vessels. While all the factors which induce this degeneration of articular cartilage are not known, wear and tear by prolonged use, mechanical stresses, overweight and trauma undoubtedly play an important rôle.

Individual variations of onset and progress of these changes are partly explained by constitutional factors. Structural inferiority of the cartilage and malformation of the joint surfaces predispose to early development of osteo-arthritis. The endocrine system, especially the hypophysis, has a powerful influence on the metabolism and growth of bone and cartilage. Imbalance of this system will induce pathologic changes. This is evidenced by the arthropathy in juveniles who suffer from lesions of the pituitary gland and by the osteo-arthritis which is associated with acromegaly. Middle and advanced ages are characterized by involution of the gonads and hypertrophy of the pituitary gland. This offers some explanation of the prevalence of osteo-arthritis among women at the menopause.

In contrast to the articular cartilage, the metabolism, blood supply and nutritional requirement of the bone are high. Consequently, bone is greatly affected by vascular lesions. Decalcification, atrophy, and even necrosis and absorption of phalanges were sometimes found in arteriosclerosis and thrombo-angiitis obliterans.

In Raynaud's disease and scleroderma, interference with the blood supply leads to a characteristic absorption of the terminal phalanges (Buerger[3]). Venous congestion in chronic heart and lung

diseases may produce hypertrophy (clubbing) of the distal phalanges, either alone or in association with toxemia (Locke[12]).

Clinical Consideration. The clinical symptomatology of osteo-arthritis confirms the conclusion that vascular changes play only a secondary rôle. The incidence of arteriosclerosis and hypertension is not much higher in patients with osteo-arthritis than in a corresponding group of the same age and sex. Kovacs *et al.*,[11] Kersley[8] and Kling[10] found that changes in the skin capillaries and skin temperature are not pronounced and not constant enough to be considered as a primary factor in the development of osteo-arthritis. The rôle of venous congestion and stasis seems to be negligible. McMasters[13] found, out of 30 cases of varicose veins with long-standing passive congestion and edema, 21 cases did not show Roentgen ray evidence of osteo-arthritis of the ankle and feet. The remaining 9 cases which showed osteo-arthritic changes had chronic ulcers of the leg. In my own material, the incidence of osteo-arthritis was not higher in patients with varicose veins as compared with patients of the same age and sex with normal veins. The results of these investigations are important for an evaluation of the efficiency for our methods of treatment of osteo-arthritis.

The most commonly used chemical, physical or electrical applications aim to increase the circulation in the joints. Recently, even surgical procedures, like drilling through the head of the femur, were recommended with this purpose in mind. The limited rôle of vascular disturbance in the pathogenesis of osteo-arthritis makes it evident that such procedures can only have a transitory symptomatic and alleviating effect, but are not sufficient to combat the underlying cause of the disease.

On the other hand, the importance of protection of the articular cartilage against excessive wear and tear is not sufficiently appreciated. Rest, correction of mechanical unbalance, and the reduction of abnormal pressure and weight-bearing offer more direct measures for prevention and checking of degenerative articular changes. As a last resort in advanced osteo-arthritis, surgical procedures, such as shelf or bifurcation operations, are justified in order completely to abolish motion or to diminish weight-bearing.

Summary. 1. The joints and blood-vessels of the lower extremities, amputated for gangrene, in 3 cases of thrombo-angiitis obliterans and in 10 cases of arteriosclerosis were studied.

2. In both groups the vessels of the extremity showed advanced lesions. The synovial vessels were normal or only moderately affected in the cases of arteriosclerosis. In thrombo-angiitis obliterans the synovial vessels were found to be more frequently involved. The synovial membrane was normal, except for localized hypertrophy in 2 cases of the arteriosclerotic group. One case of thrombo-angiitis obliterans showed subacute synovitis of ankle and knee joints. Venous congestion of the synovial membrane was found in 1 case.

3. Pronounced osteo-arthritis was present in only 2 cases. Slight erosions of the articular cartilage were found in all cases past 40 years. The incidence and extent of these changes correspond to that usually found in a similar age group with normal blood-vessels. On the basis of these findings the vascular theory of osteo-arthritis is contradicted.

4. On the other hand, articular cartilage is damaged by wear and tear of use, and by abnormal pressure, and weight-bearing. Age, mechanical and traumatic factors, therefore, play an important rôle in the development of osteo-arthritis. Constitutional inferiority of bone and cartilage or malformations of the bearing surfaces are apt to hasten and accentuate the development of osteo-arthritis. Cartilage and bone growth are profoundly influenced especially by the hypophysis. Imbalance and dysfunction of the endocrine system in advanced age and especially at the menopause explain the onset of osteo-arthritis and the prevalence in women past 40.

5. Bone has a higher metabolic rate and nutritional requirements, and is therefore susceptible to vascular disturbances. Atrophy, decalcification and, in extreme cases, also necrosis and absorption occur in arteriosclerosis, thrombo-angiitis obliterans, Raynaud's disease and scleroderma. Bone hypertrophy of the end phalanges, due to venous congestion, is quite common in chronic heart and lung diseases.

6. Clinical evidence also shows that vascular disturbance is only a secondary factor in osteo-arthritis. Organic or functional changes of the blood-vessels, blood pressure, and flow, and changes in the skin capillaries are not much more frequently found and are not more pronounced than in patients of a corresponding age group which do not suffer from osteo-arthritis.

7. Therapeutic measures to augment the circulation in osteo-arthritis are not directed against the primary cause; therefore the effect is mostly transitory and only symptomatic.

8. Protection of the joint by rest, correction of abnormal pressure, weight-bearing and, as a last resort, operative procedures which eliminate or decrease motion, offer a more efficient way of prevention and arresting of the degeneration of articular cartilages.

9. Imbalance and dysfunction of the endocrine system and especially a preponderance of the hypophysis at the menopause is a factor in the development of osteo-arthritis. It is hoped that advance in endocrine therapy will open new possibilities of combating osteo-arthritis.

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SPECIFIC TREATMENT OF PNEUMOCOCCUS TYPE II PNEUMONIA.

INCLUDING THE USE OF HORSE AND RABBIT ANTIPNEUMOCOCCUS SERUMS AND SULPHANILAMIDE.

By JOHN W. BROWN, M.D.,

ASSISTANT IN MEDICINE, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL; AND RESIDENT PHYSICIAN, UNIVERSITY OF CALIFORNIA HOSPITAL, SAN FRANCISCO, CALIF. (FORMERLY ASSISTANT RESIDENT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY).

AND

MAXWELL FINLAND, M.D.,

ASSOCIATE IN MEDICINE, HARVARD MEDICAL SCHOOL; ASSISTANT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, AND JUNIOR VISITING PHYSICIAN, BOSTON CITY HOSPITAL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

Most workers with extensive experience have succeeded in demonstrating quite regularly a striking reduction in death rate with specific serum therapy in cases of pneumococcus Type I pneumonia. The results in cases due to the Type II pneumococcus have varied with different observers, most of whom could demonstrate only slight reductions in mortality.[1a,b,2,5a,b,12,13] Widely divergent results have been reported in different years from the same clinic. Thus, at Bellevue Hospital almost no appreciable effect on the death rate was noted over a period of 5 years, but in the sixth year there were only 3 deaths among 21 treated cases (14.3%) as compared with 13 deaths among 20 controls (65%). During that year only patients admitted to the hospital within 72 hours of the onset were included in the study and every alternate case was given specific serum.[2] At the Boston City Hospital, the mortality in the cases treated with serum was 23% during 1929–32 as compared with 42% during the following 3-year period. This difference was ascribed to the marked discrepancy in the dosage employed in these 2 periods, the average dose of antibody per patient being 3 times as great in 1929–32 as in the following 3 years.[5a] A considerably larger number of cases of pneumococcus Type II pneumonia have been treated with specific antibody at the Boston City Hospital

since the time of the last report. It is of interest to present the results of therapy in these cases which include a small number treated with rabbit antipneumococcus serums and others treated with a combination of specific serum and sulphanilamide.

Patients, Materials and Methods. In general, the choice of patients for treatment with serum, the methods of pneumococcus typing and of serum administration, the selection of cases for supplementary treatment with sulphanilamide, and the manner in which this drug was used were all essentially the same as those employed in the Type I cases and are described in the previous paper.[4] Only the features pertaining to the Type II cases will be noted.

Attention has previously been called to the close association of the Type II pneumococcus with primary lobar pneumonia in adults.[5b,6] This has been fully corroborated by the more recent experience. Among 500 patients from whom this organism was obtained during the past 9 years at the Boston City Hospital, 452 (90.4%) were adults with pneumonia. In only 17, or less than 4% of the latter, was the pulmonary lesion atypical (bronchopneumonia) and almost all of these were cases first diagnosed at autopsy and were secondary to other serious disease. On the other hand, only 4% of the cases of Type II pneumococcus lobar pneumonia were "secondary." In only 10 instances (2%) was this type obtained from sputum or from pharyngeal cultures of persons without acute pneumonia. All the remaining cases were either admitted with empyema (4%) or the organism was obtained from a focal suppurating lesion (3.6%).

Reliability of Neufeld Typing. In the past 3 years a diagnosis of Type II pneumococcus made directly from the sputum by the Neufeld method proved to be wrong in only 1 instance (both the heart's blood of the mouse inoculated with the same sputum and the patient's blood culture proved to be Type I); and 4 sputa containing Type II pneumococci were incorrectly typed by this method, the proper type being discovered by mouse inoculation of the same specimen and by direct examination of subsequent specimens. (These were originally called Types I, V, VII and VIII, respectively, and given serum for these types until the correct type was determined.) In 6% of sputa from cases of Type II pneumonia, the direct examination by the Neufeld method failed and the type was obtained from the same specimens after mouse inoculation.

Serums. A total of 70 lots of concentrated Type II antiserums were used during this 3-year period. These included 64 horse serum lots varying in potency from 1000 to 3000 units of Type II antibody per cc., as compared with the National Institute of Health standard serum P11, to which a value of 150 Type II units per cc. has been assigned. Of these, 21 contained less than 1500, 26 had between 1500 and 2000, and 17 had more than 2000 units per cc. Only 9 of these were monovalent, the rest contained Type I antibodies in the same or up to 3 times the concentration of Type II units. The 6 lots of concentrated rabbit serum used ranged in potency from 4000 to 9000 units per cc.

Dosage. The total initial dose for young adults with sterile blood cultures treated before the end of the fourth day of the disease was usually 80,000 to 100,000 units. This was given in the same manner as the Type I serums, except that somewhat larger volumes were frequently given for the second or subsequent injections. Larger doses were given under the conditions previously noted for Type I cases.[4]

Results. *Gross Mortality.* The death rates during the last 3 years among the serum treated and non-serum treated cases are shown in Table 1. The figures for the 2 previous 3-year periods are included

for comparison, and the percentage of serum recipients among all cases in which the diagnosis of pneumococcus Type II pneumonia was made during life are also given. While the death rates have varied widely during each of the past 3 years among both the

TABLE 1.—MORTALITY AMONG CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA AT THE BOSTON CITY HOSPITAL.

Years.	Serum treated.			Non-serum treated.			Serum treated, %
	No.	Died.	Died, %	No.	Died.	Died, %	
1929–32	48	11	23	89	40	45	35
1932–35	38	16	42	43	20	46	47
1935–36	43	5	12	33	8	24	57
1936–37	52	15	29	19	8	42	73
1937–38	53	8	15	12	7	58	82
1935–38	148	28	19	64	23	36	70
1929–38	234	55	24	196	83	42	54

In this and in subsequent tabulations of death rates, none of the cases treated with serum are excluded. Those non-serum treated fatal cases in whom the Type II pneumococcus was first identified from autopsy material were excluded. There were 8 such cases in each of the 2 earlier 3-year periods and 3, 1 and 2 cases, respectively, in the 3 succeeding years.

serum treated and the non-serum treated cases, they have remained consistently and significantly lower among those treated with serum. This has been true in spite of the steady increase in the proportion of cases so treated. It is to be borne in mind, however, that the

TABLE 2.—INCIDENCE OF BACTEREMIA AND ITS RELATION TO THE DEATH RATE IN CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA (BOSTON CITY HOSPITAL).

Years.	Serum treated.							Non-serum treated.						
	Bacteremic cases.			Bacteremic, %.	Non-bacteremic cases.*			Bacteremic cases.			Bacteremic, %.	Non-bacteremic cases.*		
	No.	Died.	Died, %.		No.	Died.	Died, %.	No.	Died.	Died, %.		No.	Died.	Died, %.
1929–35[a]	29	18	63	34	57[1]	9	16	53	38	72	40	79[40]	22[12]	28
1935–36	13	3	23	30	30[1]	2[1]	7	9	6	67	27	24[1]	2	8
1936–37	20	10	50	38	32	5	16	7	7	100	37	12[4]	1[1]	8
1937–38:														
Horse	20	7	35	45	24	1	4	5	5	100	42	7	2	29
Rabbit	4	0	0	44	5	0	0							
1935–38	57	20	35	39	91	8	9	21	18	86	39	43[5]	5[1]	29
1929–38	86	38	44	37	148[2]	17[1]	12	74	56	76	39	122[45]	27[13]	22[29]

* Include cases in which no blood cultures were made. The numbers are shown by superscripts.

non-serum treated cases are not really controls, as already noted in the previous paper.[4] Some of the more significant factors concerned in the death rates will be considered in order to shed some light on the differences observed.

Bacteremia. The incidence of bacteremia and its effect on the death rates are shown for the different years in Table 2. It will be seen that the low death rate among both the serum treated and non-serum treated cases in 1935–36 was associated with a relatively low incidence of bacteremia in each instance. During the following year, the higher death rate among the serum treated cases accompanied the inclusion of a large proportion of cases in which serum treatment was begun late in the disease (see Table 5). In the last year, a small number of cases were treated with rabbit serums. There were no deaths among these cases. However, the death rate among the cases treated with horse serums during the same year was also low.

TABLE 3.—RESULTS OF MULTIPLE BLOOD CULTURES IN CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA. (BOSTON CITY HOSPITAL, 1935–38).

	Number of cases.	
	Recovered.	Died.
Multiple blood cultures before the first dose of serum (50 cases).		
All positive	8	6
First negative, later positive	7	1
All negative	24	4
First positive, later negative	0	0
Results of multiple blood culture in relation to treatment in 17 fatal cases.		
Positive before and after serum	..	8*
Positive before serum and negative later	..	2
Negative before and after serum	..	3
Negative before serum and positive later	..	4
Multiple blood cultures during the acute disease in non-serum treated cases.		
All negative	7	0
First negative, then positive	1	1
First positive, then negative (fatal cases)	..	3
Two or more positive	0	8

* In 2 of these cases the blood cultures were negative for several days after treatment was begun and later ones were again positive.

During 1929–32, a number of cases not treated with serum developed bacteremia while under observation, but no cases were encountered in which positive blood cultures were first obtained after serum treatment was begun.[6] Two such cases were subsequently noted.[5] The significant results in the cases in which multiple blood cultures were done during the past 3 years are shown in Table 3. The 14 cases whose earlier cultures were negative and who later had positive cultures are of special interest. The bacteremia first appeared before serum was given in 8 of these cases and after serum treatment in 4. One of the former and all the latter died. The other 2 cases received no serum and 1 died. Among the bacteremic non-serum treated cases, 3 died in spite of the fact that later cultures of the blood were sterile.

Age. The distribution of cases by decades is shown in Table 4. A large number of cases treated with serum were in the older age

groups. There were relatively more cases in the older age groups among the non-serum treated cases, but a greater proportion of the younger serum treated cases had positive blood cultures. The usual increase in mortality and in the incidence of bacteremia with

TABLE 4.—INFLUENCE OF AGE ON DEATH RATE IN CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA (BOSTON CITY HOSPITAL, 1935–38).

Age group, yrs.	Serum treated.*							Non-serum treated.						
	Bacteremic.		Non-bacteremic.†		All cases.			Bacteremic.		Non-bacteremic.†		All cases.		
	No.	Died.	No.	Died.	No.	Died.	Died, %.	No.	Died.	No.	Died.	No.	Died.	Died, %.
12–19	7[1]	0	18[3]	0	25[3]	0	0	0	..	11	0	11	0	0
20–29	4	1	17	0	21	1	5	1	1	2	1	3	2	67
30–39	14[2]	1	22[2]	1	36[4]	2	6	2	1	11	1	13	2	15
40–49	15	8	18[1]	2	33[1]	10	30	5	4	12	2	17	6	35
50–59	7	4	6	2	13	6	46	7	6	4	1	11	7	64
60–69	10[1]	6	8	3	18[1]	9	50	4	4	3	0	7	4	57
70+	0	..	2	0	2	0	0	2	2	0	..	2	2	100
Total	57[4]	20	91[5]	8	148[9]	28	19	21	18	43	5	64	23	36

* Includes cases treated with rabbit serum; the numbers are indicated by superscripts.
† Includes cases in which blood cultures were not done. (See Table 2.)

TABLE 5.—INFLUENCE OF THE DURATION OF THE DISEASE WHEN SERUM TREATMENT WAS BEGUN ON THE DEATH RATE IN CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA.

	Years.	Day treatment begun.								
		Fourth day or before.			Fifth day.			Sixth day or later.		
		No.*	Died.	Died, %.	No.*	Died.	Died, %.	No.	Died.	Died, %.
Bacteremic cases	1929–35	18	10	56	5	3	60	5	5	100
	1935–36	12	3	25	1	0	0	0		
	1936–37	12	3	25	2	1	50	6	6	100
	1937–38	17[4]	5	29	3[1]	1	33	4	1	25
	1935–38	41	11	27	6	2	33	11	7	64
	1929–38	59	21	*36*	11	5	*45*	16	12	*75*
Non-bacteremic cases	1929–35	36	5	14	12	1	8	10	3	30
	1935–36	30	2†	7	0	..	..	0		
	1936–37	28	4	14	3	1	33	1	0	0
	1937–38	22[4]	0	0	2	0	0	5	1	20
	1935–38	80	6	8	5	1	20	6	1	17
	1929–38	116	11	*10*	17	2	*12*	16	4	*25*
All cases	1929–35	54	15	28	17	4	24	15	8	53
	1935–36	42	5	12	1	0	0	0		
	1936–37	40	7	18	5	2	40	7	6	86
	1937–38	39[8]	5	13	5[1]	1	20	9	2	22
	1935–38	121	17	14	11	3	27	17	8	47
	1929–38	175	32	*18*	28	7	*25*	32	16	*50*

* The superscripts represent the numbers of cases treated with rabbit serums.
† Includes 1 case in which blood culture was not done.

advancing age is apparent among both the serum treated and non-serum treated cases.[15] The death rates are generally lower among the serum treated cases in all age groups. The age distribution of the cases treated with rabbit serums was generally favorable.

Influence of the Time of Beginning Treatment. This is shown in Table 5. The greatest increase in death rate occurred when treatment was begun after the fifth day. The results of serum treatment begun after the fourth day were more favorable during the last year than in previous years. Treatment in the rabbit serum recipients was begun before the fifth day in all but 1 of the cases.

TABLE 6.—ANALYSIS OF THE AVERAGE DOSES OF SPECIFIC ANTIBODY USED IN THE TREATMENT OF CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA (BOSTON CITY HOSPITAL, 1935–38).*

	1935–36.	1936–37.	1937–38. All cases.	1937–38. Horse serums.	1937–38. Rabbit serums.
Volume per patient (cc.)	72	121	105	116	49
Units† per patient (thousands)	125	215	189	171	277
Units per cc. of serum	1740	1880	1800	1480	5650
Number of injections	4.0	6.3	5.5	5.7	3.8
Initial injection‡	8	8	8	8	6
Subsequent injections	39	40	40	35	98
Outcome:					
Recovered	150	209	186	154	277
Died	125	231	237	237	
Blood culture before treatment:					
Negative	114	109	166	153	236
Positive	150	305	216	194	328
Treatment begun:					
Fourth day or before	125	224	191	131	301
Fifth day	120	208	212	245	80§
After fifth day	..	171	166	166	
Age groups: 12–29 years	103	138	119	118	120
30–49 years	134	252	202	171	320
50+ years	156	206	250	228	540§
Average age (years)	35.1	39.4	38.5	39.6	32.7

* During 1929–32, the average amounts used were 169 cc. containing 453,000 units or 2680 units per cc.; during 1932–35 the average dose was 145 cc. containing 136,000 units or 940 units per cc.[5a]

† The actual titrated units as standardized against the National Institute of Health standard serum P11 to which a value of 150 units of Type II antibody per cc. has been assigned. The values given on the labels were usually from 10 to 25% lower than these actual values.

‡ The figures from here down, except those in the lowest line, all represent thousands of units.

§ One case only.

Dosage. The average doses of Type II antibody used during the past 3 years are analyzed in Table 6. The average concentration of antibody in the serums used during this period was intermediate between that of the specially prepared and highly potent preparations available during 1929–32 and those of rather low potency used during 1932–35.[5a] Bacteremic patients received larger doses than non-bacteremic patients. While it was our purpose, in general, to give more antibody to patients in the older age groups and to those in whom treatment was delayed, a number of such patients were in such poor condition that the contemplated dose could not

be completed. In a few patients requiring large amounts of antibody, the treatment had to be discontinued because the available supply was exhausted. The rabbit serums had 4 times the concentration of antibody contained in the horse serums. Patients treated with the former received considerably larger amounts of antibody than those treated with horse serum, and these larger amounts were contained in a much smaller volume.

Clinical Response. The effect of serum treatment on the course of the disease was as striking during the past 3 years as was previously observed during the 1929–32 period.[6] During 1935–38, 98 (86%) of the 114 serum treated patients who recovered without purulent complications were free of fever (oral temperature 100° F. or higher) and other symptoms of the acute disease within 48 hours after the first injection of serum, and 71 (62%) had a characteristic crisis within 24 hours of beginning treatment. During the same period only 12 (29%) of the non-serum treated cases who recovered had a similar change in the clinical condition within 48 hours of admission to the hospital and 50% were febrile and acutely ill 4 or more days in the hospital.

Among the 28 fatal serum treated cases, 6 died within 24 hours after the first dose of serum was given and 17 died more than 48 hours later. Of the 23 non-serum treated deaths, 7 occurred within 24 hours of admission and 14 occurred on the third day in the hospital or later.

Untoward Reactions. Both the immediate and the delayed reactions were somewhat more frequent and more severe than those encountered in the Type I cases during the same period.[4] This may have been due to the fact that more injections were given to each patient and a greater volume was introduced with each of the individual injections, except for the initial ones (see Table 6). The incidence of the various reactions observed is summarized in Table 7.

Immediate reactions occurring during the injection or within a few minutes were observed in 42 patients treated with horse serum. Nausea and/or vomiting was the most frequent and usually accompanied by injection of lots of serum which gave chills frequently on the same or in other patients. In 2 of these cases the skin test with normal horse serum was positive and in a third the vomiting accompanied a skin eruption. In 5 instances the nausea and vomiting accompanied the first dose, but in the others it occurred only with later injections. Urticaria occurred with the initial injection in only 2 cases; in the others, it accompanied later ones. It first appeared in some cases after the fifth or sixth injection. In 4 instances it recurred after 2 or more injections. Among the patients with urticaria or asthmatic reactions, 4 had positive skin reactions, 3 had a recent history of serum injection (including one with a positive skin test) and 3 gave a previous history of asthma. Two patients complained of severe joint pains during each injection which subsided immediately after it was completed. Of the 23 patients who had immediate reactions, other than nausea and vomiting, 11 had serum sickness later. Circulatory collapse with pulmonary edema occurred during or shortly after the injection of horse serum in 2 instances and of rabbit serum in 1. One of the former was in poor general condition at the time and died after a few hours; the

others responded readily to stimulants. No other immediate reactions were observed with the rabbit serums.

Thermal Reactions. The frequency of these reactions varied from year to year. They were more common and more severe after the serums supplied by the State than after the Lederle serums that were available for clinical trial. They most frequently followed only 1 of the injections, which was usually one of the larger doses. Two of these reactions were severe and were followed by high fever (107° F.) but responded readily to treatment. There were 4 instances in which several injections of one lot of serum were given without untoward reactions and a chill occurred after the first injection of another lot of serum. In 3 patients treated with horse serums and in 1 treated with rabbit serum, the chill followed the initial intravenous injection after a larger amount had previously been given intramuscularly without febrile reaction. Aspirin (10 to 20 grains) was given before the injections in a number of instances during the last year. One or more chills occurred in 6 patients in spite of this drug.

TABLE 7.—UNTOWARD REACTIONS FROM THE USE OF SPECIFIC SERUM IN THE TREATMENT OF PNEUMOCOCCUS TYPE II PNEUMONIA (BOSTON CITY HOSPITAL, 1935–38).

	Horse serums (139 cases).	Rabbit serums (9 cases).
Immediate reactions	40 (29%)	1
Nausea and/or vomiting	17	0
Marked dyspnea or asthma	6	0
"Collapse" with pulmonary edema	2	1
Urticaria	13	0
Joint pains	2	0
Thermal reactions	60 (43%)	5
One chill	44	2
Two chills	11	3
Three chills	5	0
After initial intravenous injection only	11	1
After first and other injections	6	3
Only after second and/or later injections	43	1
Lederle lots on clinical trial (horse, 66 cases; rabbit, 9 cases)	14 (21%)	5
1935–36 (12 cases)	6 (50%)	
1936–37 (24 cases)	5 (21%)	
1937–38 (horse, 30 cases; rabbit, 9 cases)	3 (10%)	5
State serums* (84 cases†)	48 (57%)	
1935–36 (32 cases)	20 (63%)	
1936–37 (34 cases)	15 (44%)	
1937–38 (18 cases)	13 (72%)	
Delayed serum sickness	44 (32%)	5
Fever only	5	2
Rash	5[1]‡	0
Arthralgia	17[1]	2
Arthralgia and rash	17[4]	1

* Including some lots on clinical trial.

† 11 cases received both state and commercial lots; 2 had chills from both.

‡ Superscripts represent cases with enlarged lymph nodes.

Serum Sickness. Arthralgia, with or without urticaria, was the most frequent symptom. Fever occurred in almost every case; in 2 of the severe cases it reached 104° F. In 1 patient the symptoms were ushered in with a chill. The duration of the serum sickness was usually 1 to 3 days, although in some cases symptoms lasted as long as 10 days. The symptoms were considered severe in 5 of the horse serum recipients and in 1 of those treated with rabbit serum. The latter had edema of the face in addition to the rash and arthralgia.

Complications Among Recovered Cases. Among the serum treated cases, 4 developed empyema requiring surgical drainage. One of these patients received rabbit serum. In 4 other patients, all of whom were treated with horse serums, pneumococci were demonstrated only in the pleural fluid at the first thoracentesis but later fluids showed no organisms on smear or culture. In 1 of the latter cases the earlier organisms were demonstrated by culture and in the other 3 they were seen only directly in the fluid but cultures of the same fluid yielded no growth. One of the latter had a sterile blood culture and the other 7 cases had positive blood cultures before serum treatment was begun. Large sterile effusions (250 cc. or more) were demonstrated by thoracentesis and culture in 4 additional patients, including 1 bacteremic rabbit serum recipient and 3 non-bacteremic patients treated with horse serum. Purulent otitis media developed in 2 cases, but only 1 of these yielded Type II pneumococci on culture. One of the empyema patients also had an abscess of the leg and purulent arthritis from which the specific organisms were cultured and which required surgical drainage. Thrombophlebitis occurred in 2 of the rabbit serum recipients. Two pregnant women, including 1 with empyema, had a miscarriage during the acute disease.

Among the non-serum treated patients who recovered, 1 had empyema requiring operation, 1 had otitis media and a third had septic parotitis. Type II pneumococci were cultured from the pleural and aural exudates but not from the parotid pus. The septic complications in the fatal cases will be considered below.

Fatal Cases. A review of the fatal cases of pneumococcus Type II pneumonia indicates that, for the most part, death was associated with the severity of the pneumonia or its complications. In the cases treated with serum, the poor general condition of the patients when treatment was begun was a major factor in many instances. No doubt the fact that the reactions were frequent with the serums available during this period militated against the use of adequate dosage and counteracted appreciably the beneficial effects of the antibody.

Among the serum treated patients 8 had evidence of peripheral vascular collapse (stupor, low blood pressure, cold clammy skin and ashen gray color) and/or beginning pulmonary edema at the time treatment was begun, and 2 of these patients had auricular fibrillation in addition. Death occurred within a few hours in 4 of these cases and in the others the condition precluded adequate serum treatment. A similar condition developed after treatment was begun in another patient with auricular fibrillation treated on the sixth day and in 1 pregnant patient. The latter had chills after each of 3 injections, delivered a stillborn baby during the third of these chills and died shortly thereafter. Meningitis was demonstrated soon after treatment was begun in 2 patients, 1 of whom proved to have endocarditis, in addition, at autopsy. In 2 other bacteremic patients, empyema was present when treatment was begun. In 1 of these, bacteremia persisted for several days and endocarditis was probably present (there was no autopsy). Alcoholism was probably directly responsible for the death in

2 cases; 1 was in coma when treatment was begun and died in 6 hours, and the other survived for several days and died in delirium tremens during extreme uncontrolled activity. There was 1 patient who was admitted for alcoholism, a fractured skull and probably fractured ribs. His pneumonia improved following treatment but he died suddenly with acute dyspnea 16 days later. In another patient, autopsy revealed a large aortic aneurysm compressing one entire lung. In the 10 remaining patients either the dosage was inadequate or there was too long a delay between injections or else the serum was ineffective. Bacteremia first developed 4 or more days after treatment was begun in 3 of these patients.

Among the fatal non-serum treated cases, 3 had empyema and 1 of these developed meningitis 3 weeks after surgical drainage. Purulent complications were present in 2 other patients; meningitis in 1 and arthritis in the other. In 1 patient the symptoms suggested perforated peptic ulcer but neither operation nor autopsy was performed. The other patients all died of uncomplicated pneumonia.

Résumé of Cases Treated With Rabbit Serum. (See Tables 2, 4, 5, 6 and 7.) Nine cases of pneumococcus Type II pneumonia were treated with rabbit serums and all recovered. The average dose was larger in terms of units but smaller in volume compared with that used in the horse serum treated cases. Four of the patients had positive blood cultures, including a woman of 67 in whom treatment was begun at the end of the fourth day and was supplemented with sulphanilamide. One other non-bacteremic patient was 43 years old, and the remaining patients were under 40. One of the bacteremic patients who received 300,000 units on the first 2 days of the disease developed empyema which required surgical drainage. Immediate reactions of the "allergic" type (urticaria and asthma) did not occur, but 1 patient developed low blood pressure, rapid pulse and slight pulmonary edema after the second and third injections but responded readily to stimulants in each instance. Chills and serum sickness were about as frequent as among the horse serum recipients.

Cases Treated With Sulphanilamide. The use of this drug in pneumococcus Type II pneumonia was reserved, in general, for the severest cases, particularly when they were seen late in the disease. Only 1 such patient was treated with the drug alone and that patient died before any appreciable amount could be given. The relevant data in 8 patients treated during 1937–38 with the combination of specific serum and sulphanilamide are shown in Table 8.

The average age of these 8 patients was 59 years. The only patient in this group who was under 50 years of age had a negative blood culture before treatment. He recovered promptly and the drug was discontinued. Bacteremia was present in 5 of the remaining 7 patients before treatment was begun and in these patients all subsequent blood cultures were sterile. Two of the 5 bacteremic patients and 1 of the non-bacteremic patients died. In the 4 patients tested, the concentration of the drug in the blood did not reach the desired level in spite of the doses used. In Case 1 the

lower level was obtained while the patient was receiving 3 gm. daily. No toxic effects of the drug was noted in these cases.

It is obviously not possible to draw conclusions from such a small group of cases, but the poor prognosis in the sort of cases selected suggests that the drug may have had some beneficial effect on the disease.

TABLE 8.—RÉSUMÉ OF CASES OF PNEUMOCOCCUS TYPE II PNEUMONIA TREATED WITH A COMBINATION OF SPECIFIC SERUM AND SULPHANILAMIDE (BOSTON CITY HOSPITAL, 1937–38).

Case.	Sex and age.	Blood cultures.	Lobes involved.	Specific serum.		Sulphanilamide.			Termination: mode, day.	Remarks, complications.
				Days.	Units, × 1000.	Days.	Total, gm.	Blood,* mg./100 cc.		
1	M 63	Pos. 3, 4, 5; Neg. 6, 7, 8	Ll	4–6	390	4–9	24	7.6–3.3	D9	Emphysema, chronic bronchitis.
2	F 57	Neg. 5, 6, 7, 10	RIlL	6–7	225	6–14	50	8.4	D14	Mild pulmonary edema after serum, then improved; sudden death (no autopsy).
3	M 68	Neg. 6, 7	Rum	6–8	120	6–11	36	6.8	C9	Jaundice and semiconscious before treatment
4	F 67	Pos. 3, 4; Neg. 5	Rl	4–5	R530	4–7	28	...	C6	Chills after 2 doses of serum.
5	M 43	Neg. 4	Ruml	4–5	R500	4	8	...	L5–8	Chill, 2d dose; severe serum sickness.
6	F 55	Pos. 3 (?), 4; Neg. 2, 5–8	Rl	3–6	520	6–8	16	...	D8	Duration uncertain.
7	M 66	Pos. 8; Neg. 6, 10	Rml	8–9	175	8–15	102	6.5	L10–14	Stormy course.
8	F 51	Pos. 2; Neg. 3, 4	Rum	2–3	250	3–8	40	...	C3	Onset with chill 11 days after crisis from Type IX pneumonia treated with sulphanilamide.

* Unheated.[10] The values for the total sulphanilamide were 25 to 50% higher.

ABBREVIATIONS: Sex: M = male, F = female. Lobes: L = left, R = right, u = upper, m = middle, l = lower. Blood cultures: Pos. = positive, N = negative for Type II pneumococci. The numbers represent the day of the disease. Termination: C = crisis, L = lysis, D = death.

Discussion. The low death rate in a comparatively large group of cases of pneumococcus Type II pneumonia during the past 3 years is most encouraging. It is particularly impressive since it was attained, for the most part, with the use of concentrated antipneumococcus horse serums and in spite of the inclusion for specific treatment of an increasing proportion of the Type II cases among which the incidence of bacteremia was high. It will be noted from Table 5 that during the last 3 years, 121 consecutive cases were treated within 96 hours of the onset of the disease with a mortality of 14%. Such a low death rate was previously noted with the use of horse serum preparations by Cecil and Plummer[2] during a single year in 21 cases admitted within 72 hours of the onset, and in 43 of Bullowa's recent cases (1934–38) treated before the fifth day.[1b]

The average dose of antibody used in these cases was not high. However, it seems to us that, except where the conditions of the patient precluded the use of larger amounts of the particular lots of serum available at the time, the quantities in individual groups of patients approached more closely than in previous years the

desired ideal in dosage, namely, that amount which is most effective and least wasteful.

The importance of untoward reactions is brought out rather strikingly in these cases. There can be little doubt that some of the individual poor results are ascribable in large measure to this factor. Repeated reactions during serum administration in severely ill patients, particularly when the serum has a low antibody content, are obviously detrimental to the patient. Valuable time is lost, the general defenses of the patient are probably lowered, and one is tempted to use insufficient amounts of the specific agent to be effective.

The results in the small number of cases of pneumococcus Type II pneumonia treated with rabbit serums are encouraging. The fact that the average potency of the rabbit serum preparations used was almost 4 times that of horse serums is most significant. While reactions have been no less frequent, the introduction of larger amounts of the specific antibody with each dose reduces the number of injections necessary to bring about the desired clinical improvement.

Obviously, the most desirable product will be the most potent concentrated antibody that can be given conveniently and with the minimum of untoward effects. The few data presented here and the good results reported from the use of unconcentrated rabbit serums in small groups of Type II cases treated by Horsfall and Loughlin and their associates[7,9] should encourage further attempts to produce potent concentrated rabbit serums for this type.

The use of sulphanilamide or similar drugs may also prove to be a valuable adjunct to the serum treatment, particularly in bacteremic cases in which treatment is begun late in the disease. They may also be useful in other cases when only serums of low potency are available. Further studies of their use in adequately controlled cases are desirable.

Summary and Conclusions. During the past 3 years, coincident with a steady increase in the proportion of cases treated with serum, the death rate among 148 serum treated cases of Type II pneumococcus pneumonia was 19%. The death rate among 64 contemporaneous non-serum treated cases was 36%; among 196 similar cases occurring since the fall of 1929 it was 42%. Only 14% of 121 cases treated with serum before the end of the fourth day died. The death rates were lower in both bacteremic and non-bacteremic cases. The greatest reduction in mortality appeared to be in patients between 20 and 60 years of age.

The deaths among the serum treated cases occurred chiefly in patients with other serious complicating conditions and in those who were in poor general condition when the treatment was begun.

Untoward reactions to serum injections were more frequent in Type II cases than in the Type I cases. The possible significance of these reactions is discussed.

Concentrated rabbit serums were used in the treatment of 9 patients, including 4 with bacteremia. None of these patients died. The relatively high potency of these Type II rabbit serums suggests that they may prove to be preferable to horse serums in the treatment of pneumococcus Type II pneumonias.

The small experience with sulphanilamide suggests that this or similar drugs may have some usefulness as an adjunct to specific serum in the treatment of certain severe Type II cases.

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SPECIFIC TREATMENT OF PNEUMOCOCCUS TYPE V AND TYPE VII PNEUMONIAS.

Including the Use of Horse and Rabbit Antipneumococcus Serums and Sulphanilamide.

By Maxwell Finland, M.D.,

Associate in Medicine, Harvard Medical School, Assistant Physician, Thorndike Memorial Laboratory, and Junior Visiting Physician, Boston City Hospital, Boston, Mass.,

and

John W. Brown, M.D.,

Assistant in Medicine, University of California Medical School, and Resident Physician, University of California Hospital, San Francisco, Calif., (formerly Assistant Resident Physician, Thorndike Memorial Laboratory).

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

In the preceding papers[1,6] we were concerned with the results of specific treatment in the pneumonias due to Types I and II pneumococci. These were the first types to be recognized and are the most frequent causes of pneumonia (with Type III, which is usually somewhat more frequent than Type II). Clinically, they are inti-

mately associated with primary and typical lobar pneumonia and they are rarely found in the nasopharynx of individuals not suffering from or exposed to this disease. Types V and VII are less frequent causes of pneumonia than the three classical types, but they are two of the three most frequent types (Type VIII is the third) classified from among the pneumococci previously included in Group IV.[3,4] They both differ from Types I and II, as well as between themselves with respect to the character of the pulmonary lesion they may produce and the relative frequency with which they are found in the nasopharynx without relation to pneumonia.[7,11]

Serums for Types V and VII have come into use only recently and reports concerning their efficacy in the specific treatment of pneumonia are still few, but such reports differ with respect to these two types in about the same manner as the differences concerning the efficacy of Type I and Type II serums. Most writers have had uniformly favorable results in Type V cases, just as in those due to Type I, but the opinions concerning the efficacy of Type VII serums have varied about as much as those concerning the value of serums in Type II cases.[2,9,12–15,18–20] Only small numbers of cases of the newer types have been included in the reports. The cases occurring at the Boston City Hospital prior to July, 1936, have been reported elsewhere.[9,12] In both the Type V and the Type VII cases the death rates in serum treated cases were considerably lower than among non-serum treated cases and marked clinical improvement occurred with considerable regularity in direct relation to serum treatment. The results of the past 2 years in a larger number of cases have fully corroborated the earlier experience. For the purpose of brevity, the data concerning the Type V and Type VII cases will be presented in parallel. The comparison between these two types will also bring out certain features of the so-called higher types of pneumococci that are of interest.[2,5,18]

Patients, Materials and Methods. In general, the choice of patients for treatment with serum or sulphanilamide, the methods of typing and of serum administration were similar to those described for the Type I cases.[6] Only those aspects that concern the Types V and VII cases specifically will be considered here. For orientation it is well to note, first, what sort of patients harbor pneumococci of these types. Diagnostic serums for Types V and VII have been available at the Boston City Hospital since the fall of 1929 and have been employed in the classification of all pneumococci that have been encountered since that time. The relative frequency with which these types have occurred in patients with pneumonia or with other conditions is shown in Table 1. Most significant is the comparatively high incidence of carriers and persons with simple upper respiratory infections among those harboring Type VII pneumococci as compared with the incidence of those from whom Type V organisms were obtained. In this respect Type V is similar to Types I and II. Equally important is the greater relative incidence of atypical pneumonias in adults. About 19% of the Type VII and 10% of the Type V pneumonias were classed as atypical pneumonias. Moreover, atypical pneumonias associated with Types V and VII pneumococci, particularly the latter, were usually primary,

in contrast to the infrequent cases of atypical Type I or Type II pneumococcus pneumonias which were almost all secondary or terminal events in the course of other serious diseases.

The atypical character of the Type VII cases and the occurrence among them of mild cases, as well as the frequent occurrence of this type in patients without pneumonia has necessitated extra caution in the choice of patients with this type for serum treatment. In those cases in which considerable pulmonary consolidation was not demonstrated and in those whose symptoms were mild, serum treatment was either omitted or postponed until the signs were more evident and the symptoms more characteristic.

TABLE 1.—PATIENTS HARBORING TYPE V AND TYPE VII PNEUMOCOCCI. (BOSTON CITY HOSPITAL, 1929–38).

	Type V.	Type VII.
Lobar pneumonia in adults	298	211
Atypical pneumonia in adults	34	48
Adults admitted with empyema	5	5
Pneumonia and/or empyema in children*	24	4
Focal purulent infections	22	18
Carriers or respiratory infections without pneumonia	8 (2%)	24 (8%)
Total	391	310
Pneumonia in adults:		
Per cent lobar	90.0	81.5
Per cent atypical	10.0	18.5
Per cent of all pneumococcic infections:		
Highest (both in 1935–36)	12.8	8.2
Lowest (V in 1929–30, VII in 1932–33)	3.8	3.6

* Not studied routinely. These cultures obtained from blood, pleural fluids or autopsy material.

Reliability of Direct Neufeld Sputum Typing.[17,21] In the past 3 years, much reliance has been based on this method for rapid typing. During this period a positive diagnosis of Type V was proved to be incorrect by mouse inoculation of the same sputum in only 4 (5%) of 82 cases in which the comparison was possible. The types of pneumococci obtained from the mouse in these 4 cases were: Types I, II (twice) and III. Likewise a diagnosis of Type VII was incorrect in 2 (3%) of 62 cases; 1 of these proved to have Type I and the other Type V by mouse inoculation. The Neufeld typing with the proper serums was interpreted as negative in 27 (25%) of sputa which yielded Type V and in 20 (23%) of those which later yielded Type VII pneumococci after inoculation into mice. In addition, 2 sputa containing Type V and 4 with Type VII pneumococci were incorrectly diagnosed as other types which were not found by other methods. One of the former was called Type III and the other was called Type VII; and the latter 4 were wrongly diagnosed Types I (2 instances), VIII and IX, respectively.

Therapeutic Serums and Dosage. The data concerning the serum used prior to July, 1936, has been included in the previous reports.[9,12] Most of the serums used since that time were prepared and furnished for clinical trial by the Lederle Laboratories, Inc. Those employed during the past two years included 25 lots of bivalent Types V and VII concentrated antipneumococcus horse serum ranging in potency from 3000 to 7000 units* of Type V and from 4000 to 12,000 units of Type VII antibodies per cc. The concentration of Type V antibody was less than 4000 units per cc. in

* The actual number of units as determined by comparison with the standard serum will be given in the text and tables. The numbers recorded on the labels were 15 to 35% lower.

7 lots, between 4000 and 5000 in 14 and over 5000 units per cc. in 4 lots. For Type VII, there was less than 5000 units of antibody per cc. in 7 lots, between 5000 and 7000 in 11 lots and 7000 units per cc. or more in 7 lots. In addition, 7 monovalent lots of concentrated rabbit serums were used, 1 containing 5500 units of Type V and the others containing from 9000 to 27,000 units of Type VII antibody per cc. Three lots of concentrated Types II and V horse serums, each containing about 1350 units of Type V antibody per cc. and 2 lots of Type VII and VIII horse serums containing 3100 and 4000 units of Type VII antibody were supplied by the Antitoxin and Vaccine Laboratory of the Massachusetts Department of Public Health.

The bivalent Type V and VII serums were usually given as follows: an initial 5 cc., 2 hours later a second dose of 15 or 20 cc. (occasionally 35 cc.) and, if necessary, 20 to 40 cc. 2 or more hours later, depending on the age of the patients and the other factors already mentioned as indicating larger doses.[6] With the other horse serums and with the rabbit serums, which were mostly experimental lots, the initial injection was 1 to 2 cc. followed, at intervals of 2 hours or more, by increasing amounts depending on the occurrence and severity of reactions. All were given intravenously, except some of the doses of rabbit serum which were given intramuscularly.

Results. *Gross Mortality.* The death rates among the cases of each type varied from year to year but were constantly much lower for the serum treated than for the non-serum treated cases. This difference persisted even in the last year when a considerably larger proportion of the cases were treated with serum as compared to previous years. The figures for the different years during which these serums have been available are shown in Table 2.

TABLE 2.—MORTALITY IN CASES OF PNEUMOCOCCUS TYPE V AND TYPE VII PNEUMONIA (BOSTON CITY HOSPITAL, 1929–38).*

Years.	Type V cases.							Type VII cases.						
	Serum treated.			Non-serum treated.			Serum treated, %.	Serum treated.			Non-serum treated.			Serum treated, %.
	No.	Died.	Died, %.	No.	Died.	Died, %.		No.	Died.	Died, %.	No.	Died.	Died, %.	
1929–33	..	..	..					..	..	..	56	14	25	0
1933–34	..	..	..	116	50	43	0	4	0	0	21	7	33	16
1934–35	..	..	..					7	1	14	9	4	44	44
1935–36	26	4	15	65	24	37	28	19	2	11	28	9	32	40
1936–37	23	1	4	42	20	48	35	14	2	14	33	7	21	30
1937–38	32	3	9	11	3	27	74	35	4	11	13	6	46	73
Total . .	81	8	10	234	97	41		79	9	12	160	47	29	

* In this table and in those that follow, all cases receiving specific serum are included regardless of the amount or the time given. From among the non-serum treated cases are excluded those in whom the pneumococcus was first identified from autopsy materials. The numbers of such cases for the various periods are: among the Type V cases: 1929–35, 14; 1935–36, 2; 1936–37, 3 (total, 19 cases); among the Type VII cases: 1929–33, 7; 1934–35, 2; 1935–36, 7; 1936–37, 3; 1937–38, 1 (total, 20 cases).

Influence of Bacteremia. In both the Type V and the Type VII cases the death rate was about 5 times as high among the patients with positive blood cultures as among those whose blood cultures

showed no growth. This was true for both the serum treated and the non-serum treated cases. The differences in death rates between the cases receiving serum and those not treated with serum was equally striking in both the bacteremic and non-bacteremic cases of each type. These death rates are shown in Table 3.

TABLE 3.—EFFECT OF BACTEREMIA ON THE DEATH RATE IN CASES OF PNEUMOCOCCUS TYPE V AND TYPE VII PNEUMONIA (BOSTON CITY HOSPITAL, 1929–38).

Result of blood culture.	Type V cases.						Type VII cases.					
	Serum treated.*			Non-serum treated.			Serum treated.*			Non-serum treated.		
	No.	Died.	% Died.	No.	Died.	% Died.	No.	Died.	% Died.	No.	Died.	% Died.
Positive	27[1]	6	21	84	67	79	16[2]	6[1]	38	32	28	88
Negative	54[1]	2	4	111	17	15	63[7]	3	5	102	16	16
Not done	..	..	..	39	13	33	..	..	..	26	3	12
Bacteremic, %	33			43			20			24		

* The superscripts indicate the number of cases treated with rabbit serums.

The cases in which multiple blood cultures were done during the acute disease or before beginning serum treatment are of interest. Those occurring before 1935 have been noted previously[7,11] and the recent ones are summarized in Table 4. The importance of making

TABLE 4.—RESULTS OF MULTIPLE BLOOD CULTURES TAKEN DURING THE ACUTE DISEASE AND BEFORE SERUM TREATMENT (1935–38).

	Type V cases.				Type VII cases.			
	Serum.		No serum.		Serum.		No serum.	
	Recovered.	Died.	Recovered.	Died.	Recovered.	Died.	Recovered.	Died.
More than 1 blood culture positive	10*	2	2*	10	0	2	0	2
First blood culture sterile, later ones positive	3	1	2	2	4	0	1*	1
All blood cultures sterile	23	0	13	3	21	2	9	5
First culture positive, later ones sterile	1	0	2	3	1	0	0	1

* One case developed empyema.

a blood culture immediately before the first dose of serum is given regardless of whether previous cultures have been made is apparent from these results. Bacteremia developed under observation in 14 cases of both types. Serum was given after the bacteremia developed in 8, of whom only 1 died, whereas of the 6 who did not receive serum, 3 died. Most significant, however, is the small

number of deaths among the Type V cases who had more than one positive blood culture and then received serum as compared with the large number of similar cases who died without receiving serum.

Influence of Age (Table 5). Deaths in patients under 20 years of age did not occur among the Type VII pneumonias and were

TABLE 5.—DEATH RATES IN CASES OF TYPE V AND VII PNEUMOCOCCUS PNEUMONIA ARRANGED ACCORDING TO AGE (BOSTON CITY HOSPITAL).

Age group, yrs.	Type V cases.						Type VII cases.					
	Serum treated, 1935–38.			Non-serum treated, 1929–38.			Serum treated, 1933–38.			Non-serum treated, 1929–38.		
	No.	Died.	Died, %.	No.	Died.	Died, %.	No.	Died.	Died, %.	No.	Died.	Died, %.
12–19	19	1	5	30	1	3	8	0	0	16	0	0
20–29	18	0	0	32	11	34	17	0	0	25	1	4
30–39	25	4	16	58	18	31	21	2	9	26	3	11
40–49	13	1	8	44	21	48	15	1	7	33	15	45
50–59	4	1	25	37	21	57	12	3	25	31	12	39
60+	2	1	50	33	25	76	6	3	50	29	16	55
Total	81	8	10	234	97	38	79	9	12	160	47	29

rare in the Type V cases. In older patients, the death rates were lower among those receiving serum than among the non-serum treated cases. Relatively few patients over 60 years were treated with serum. The number of treated cases in the various age groups is too small to indicate the full effect of age on mortality as was shown among the serum treated Type I and II cases[1,6] and in the present non-serum treated cases.

Influence of the Time When Serum Treatment Was Begun. The importance of early treatment is indicated by the death rates for cases treated on various days after the beginning of the pneumonia as shown in Table 6. Treatment with serum was equally effective,

TABLE 6.—INFLUENCE OF THE DURATION OF THE DISEASE AT THE TIME SERUM TREATMENT IS BEGUN ON THE DEATH RATES IN CASES OF PNEUMOCOCCUS TYPE V AND TYPE VII PNEUMONIA (BOSTON CITY HOSPITAL).

Day treatment begun.	Type V cases.*			Type VII cases.*		
	No.	Died.	Died, %.	No.	Died.	Died, %.
Fourth or earlier	67^{20}	5^{3}	7	60^{8}	2^{1}	3
Fifth	7^{2}	0	0	9^{2}	0	0
Sixth	3^{2}	1^{1}	33	5^{1}	2	40
Seventh and later	4^{3}	2^{2}	50	5^{5}	5^{5}	100

* The superscripts represent the number of bacteremic cases included.

insofar as indicated from the low death rates, when treatment was begun on or before the fifth day. The cases treated after that time are too few to be highly significant, however, particularly since patients seen later in the disease were generally not treated with serum if they appeared to be improving and the results of blood

cultures were known to be negative. The fatalities occurred primarily in the late bacteremic cases.

Dosage. The average doses of antibody used are analyzed in Table 7. The concentration of antibodies in terms of units was considerably greater in the Types V and VII serums than in those for Types I and II. This permitted the administration of much larger amounts of antibody, in a smaller total volume, and with fewer injections. Since the units of antibody are based on protection of mice against the specific organisms the unit for any one type of pneumococcus is not necessarily comparable in its therapeutic

TABLE 7.—SUMMARY OF THE AVERAGE DOSES OF SPECIFIC ANTIBODY USED IN CASES OF TYPE V AND TYPE VII PNEUMOCOCCUS PNEUMONIA AT THE BOSTON CITY HOSPITAL.

	Type V. (81 cases*).	Type VII. Horse serums (70 cases).	Type VII. Rabbit serums. (9 cases).
Volume (cc.)	43	39	43
Units† (thousands)	150	209	530
Units per cc.	3490	5360	12,300
Number of injections	3.4	3.2	3.2
First injection (thousands of units)	17	25	12
Subsequent injections	55	84	235‡
Total dose per patient:			
Non-bacteremic cases	116	173	360
Bacteremic cases	219	264	1130
Recovered cases	147	195	480
Fatal cases	162	319	1260
Age: Less than 30 years	131	185	225
30–49 years	157	215	585
50 years and older	205	224	930
Average age (years)	31.4	37.6	39.2

* Nine patients were treated with some of the first lots of this type prepared by the State laboratory. The average dose in these patients was 127 cc., containing 231,000 units (1835 units per cc.) in 6.8 injections. If these cases are omitted the average dose in the remaining cases was 32 cc., containing 140,000 units (4375 units per cc.) given in 3 injections. Concentrated rabbit serums were used in 2 Type V cases, including 1 bacteremic patient. Each received 17 cc. containing 85,000 units in 2 injections. (See footnote p. 383.)

† Compared with standard serum L1, maintained by the Lederle Laboratories, Inc., to which was assigned a value of 150 units of Type V and 300 units of Type VII antibody per cc.

‡ The intramuscular route was used to give virtually the entire dose in 2 patients and part of the dose in 2 others.

efficacy in man to that of any other type. However, the use of standard serums in the evaluation of the potencies permit, within any given type, the most uniform comparison that can be made with the available methods. Larger doses, in terms of these units, were necessary for Type VII than for Type V cases, but the serums were proportionally more concentrated. As with other types, larger doses were used in bacteremic and in older patients.

Untoward Reactions. The various types of untoward reactions observed following serum therapy in both the Type V and the Type VII cases were similar in character and frequency to those

observed in the serum treated Type I case.[6] They are listed in Table 8.

The reactions classed as "immediate" occurred during the injection or at varying intervals up to 1 or even 2 hours later. About one-half of them were associated with the initial injections, while some occurred only after 2 or more uneventful injections. Only 2 patients experienced such reactions after each of 2 or more injections. In 2 patients who were almost moribund when treatment was begun, death followed within a few minutes of an injection (the second and sixth, respectively). All the thermal reactions were mild or moderate. Only 2, each following injections of experimental lots of rabbit serum, were followed by fever of 106° F., or higher, and these responded promptly to treatment. Serum sickness was mild in most cases and moderate in a few. Fever to 100° or 101° F. accompanied the urticaria and arthralgia in most, but not all, of the cases.

TABLE 8.—OCCURRENCE OF UNTOWARD REACTIONS IN PATIENTS WITH TYPE V AND TYPE VII PNEUMOCOCCUS PNEUMONIAS TREATED WITH SPECIFIC ANTIBODY (BOSTON CITY HOSPITAL).

		Type VII.	
	Type V. (81 cases).	Horse serums (70 cases).	Rabbit serums (9 cases).
Immediate reactions	11 (14%)	12 (17%)	2
Nausea and/or vomiting	3	3	
Urticaria	5	2	
Dyspnea, cyanosis, asthma	1	5	
Fainting (collapse)	1	1	1
Chill during injection	1	1	1
Thermal reactions	21 (26%)	6 (9%)	5
After 1 injection only	16	6	3
After 2 or more injections	5*	0	2
Only after the first injection	4	1	1
After first and later injections	3*	0	2
Only after second and/or later injections	14	5	2
Delayed serum sickness	21 (26%)	23 (33%)	1
Fever only	2	2	
Urticaria	3	5†	
Arthralgia	11†	9	
Arthralgia and urticaria	5	7	1

* Including 1 rabbit serum recipient.
† Includes 1 with adenopathy in addition.

Clinical Response. Prompt crisis followed serum treatment in most of the cases. Among the 68 Type V cases who recovered without purulent complications, 48 (71%) had a crisis within 24 hours and only 3 were ill more than 48 hours after the first injection of type specific antibody. Only 14 (21%) of the corresponding non-serum treated cases were clinically improved within 24 hours after admission to the hospital.

Among the Type VII cases, 45 (64%) of those who recovered had a crisis within 24 hours and 8 (11%) more were afebrile within 48 hours of the first dose of serum. In some of the remaining patients there were mixed infections, but in 10 of the cases, including the 2 who received the entire dose of rabbit serum intramuscu-

larly, the course of the disease was not demonstrably influenced by what were considered to be moderately large doses of antibody, and no cause for these possible failures was detected.

Complications. Purulent complications were demonstrated after serum treatment in 8 (10%) of the Type V cases. They included empyema 5, bilateral otitis media 1, and pelvic abscess 1. Only 1 of these patients died and vegetative endocarditis was found in addition to the empyema in this patient. Three of the patients with empyema and the one with the pelvic abscess had positive blood cultures before treatment was begun. Serofibrinous pericarditis was demonstrated in 1 of the fatal serum treated patients who had active rheumatic heart disease. Among the contemporaneous non-serum treated Type V patients 15 (12%) had empyema and 11 of them died. In 6 of the 11 fatal cases, other complications were also found, including endocarditis in 3, and pericarditis, meningitis and lung abscess, each in 1 case. One additional patient had rheumatic heart disease and was found to have vegetative endocarditis at autopsy. There were 8 pregnant women among the serum treated patients, including 3 who died during or after miscarriage, and 1 who developed empyema and whose pneumonia probably began during or just before a normal delivery. The pregnancy proceeded uneventfully into convalescence in the other 4 patients. One of the non-serum treated patients died soon after the premature delivery of a normal live baby.

Purulent complications were relatively uncommon among the Type VII patients. Meningitis was present on admission in 1 of the serum treated patients and autopsy disclosed, in addition, the presence of vegetative endocarditis. The latter was probably also present in 2 other patients who had persistently positive blood cultures and developed cardiac murmurs after serum treatment, but there were no embolic phenomena recognized and no autopsies obtained in these patients. Frank empyema developed in 2 non-serum treated patients and meningitis in 1; the latter and 1 of the former died.

Serofibrinous effusions which resorbed spontaneously were demonstrated in 3 serum treated and in 2 non-serum treated Type VII patients who recovered. In 1 of the former, organisms resembling pneumococci were seen in smears of the first fluid, and in 1 of the latter Type VII pneumococci were cultured from the first fluid withdrawn. In 1 of the serum treated patients, a 7 months' pregnancy was unaffected, whereas 1 of the non-serum treated patients miscarried a 3 months' fetus before crisis.

Fatal Cases. The essential details concerning the serum treated patients who died prior to July, 1936, have been recorded elsewhere.[9,12] Death in each instance was associated with late or inadequate treatment or with serious complicating factors. The same was true during the past 2 years.

Of the 4 recent fatal serum treated Type V cases, 3 were bacteremic and in extremis when the first dose of serum was given and lived only a few hours thereafter. One of them had rheumatic heart disease and auricular flutter, and autopsy disclosed a vegetative endocarditis. The fourth patient was 4 months pregnant and developed increasing pulmonary edema following serum administration and died 2 days later during labor. The blood culture on the day of death showed hemolytic streptococci.

Among the serum treated Type VII patients who died during the last 2 years, 1 had meningitis on admission and autopsy revealed endocarditis in addition. Two patients in whom serum treatment was begun late in the disease continued to have positive blood cultures following large doses of serum and endocarditis was suspected but no autopsies were obtained.

TABLE 9.—RÉSUMÉ OF RELEVANT DATA IN CASES OF TYPE V AND TYPE VII PNEUMOCOCCUS PNEUMONIA IN WHICH SULPHANILAMIDE WAS USED.

Case	Type.	Sex and age.	Blood cultures.	Lobes involved.	Specific serum.		Sulphanilamide.			Termination: mode, day.	Remarks.
					Days.	Units × 1000.	Days given.	Total gm.	Mg./100 cc. in blood.*		
1	V	F 30	Pos. 1; Neg. 2, 3, 5	Lu	2–4	320	5–7	16	...	C6	Sore throat 4th day.
2	V	M 14	Neg. 4	Rl	..	..	11–20	33	...	L22	S.H. in sputum and in 4 pleural fluids; anemia; transfusion 500 cc. on 18th and 24th days; no operation.
3	V	M 46	Pos. 6; Neg. 8, 9, A	Ruml	..	..	6–9	27	...	D9	S. aureus and H. influenzæ (no pneum.) found at autopsy.
4	VII	F 19	Neg. 4, 8, 10, 12	RlLl	4–7	560	9–14	24	6.0	C13	S.H. and Pn. VII in sputum 10th day.
5	VII	M 52	Pos. 9, 11, 12, 13, 14, 15	Ruml	11–14	420	13–15	20	7.5	D15	Pericardial rub and systolic murmur 14th day.
6†	VII	F 43	Pos. 28 (?), 29, 30, 31, A	Ru	29–31	530	26–31	42	4.6;5.1	D32	Meningitis and endocarditis.

* The levels after heating were 1 to 2.5 mg. higher.[18]

† The details in this case and another case of meningitis without pneumonia are recorded elsewhere.[19]

ABBREVIATIONS: Sex: M = male, F = female. Lobes: R = right, L = left, u = upper, m = middle, l = lower. Blood cultures: Pos. = positive, Neg. = negative for the homologous type of pneumococcus, the numbers represent the day of disease, A = autopsy culture of heart's blood. Termination: C = crisis, L = lysis, D = died. Remarks: S.H. = hemolytic streptococci.

A fourth patient with uremia (100 mg. non-protein nitrogen per 100 cc. of blood before serum treatment) died 24 hours after serum was given. The fifth patient, a 56-year-old colored man, had a growth of about 4000 colonies of Type VII pneumococci per cc. of blood before treatment, which, according to the history, was undertaken on the second day. He was in very poor condition and died during the second injection of serum. The sixth fatal case was a 64-year-old man with bacteremia and auricular fibrillation who was treated with rabbit serum on the fourth and fifth day of illness. He was considerably improved but died suddenly while attempting to get out of bed 5 days later.

Résumé of Cases Treated With Rabbit Antipneumococcus Serums. Concentrated type-specific rabbit serums were used in the treatment of 2 cases of Type V and 9 of Type VII pneumococcus pneumonia. The 2 Type V patients were 14 and 20 years of age, respectively.

The latter had a positive blood culture before treatment. Each received 85,000 units in 2 injections and recovered promptly. A chill occurred after each dose in 1 of the patients. Among the Type VII patients 2, including the 1 fatal case, had positive blood cultures. Large amounts of antibody were given (see Table 7). Chills occurred in 5 patients and necessitated administration by the intramuscular route for part or almost all the serum in 4 patients. One patient had a marked drop in blood pressure and "collapse" following an intravenous dose. Serum sickness developed in only 1 patient (see Table 8). The 2 patients who received practically all their serum intramuscularly were acutely ill for 4 or more days after treatment, whereas 5 of the 6 remaining patients who recovered had a crisis within 12 hours and the sixth within 22 hours after the first injection of serum.

Sulphanilamide. The significant data in 6 cases treated with the drug alone or with specific serum are shown in Table 9. In general, the drug was used only in cases with complicating hemolytic streptococcal infections or when bacteremia occurred late in the disease. In Case 2, the hemolytic streptococcal empyema was treated by repeated thoracentesis and did not require other operative interference. In Case 3, no pneumococci could be recovered from the lungs at autopsy, although they were cultured from the blood 3 days previously, before any of the drug had been given. The data in Case 5 and Case 6 would indicate that the bacteriostatic action is not adequately effective with bacterial endocarditis, at least with the doses of the drug used.

Discussion. The results presented in this paper indicate the sort of effects that specific serums may be expected to yield in the treatment of cases of pneumonia due to the so-called "higher types" of pneumococci. The Type V cases represent a group in which the organism is definitely related to the pulmonary infection with great regularity, just as in cases with Types I and II pneumococci. The specific serums for Type V are potent and uniformly effective. The failures are definitely accounted for by causes apart from the specific action of serum.

Type VII pneumococcus, on the other hand, represents a type which like Type III[5,8] may be present frequently in sputum or pharyngeal cultures when there is no pneumonia present or where there is only a simple infection of the upper respiratory tract. Under such conditions the finding of this organism in any given case of pneumonia may be misleading and may mask the true etiologic agent. Treatment directed against this organism under such circumstances will be of no avail, as indicated in a number of the recent cases. When the organisms are found regularly, in large numbers as the only apparent agent, the disease should be favorably influenced by specific serum. Other causes residing in

the organism, the serum, or the patient may be responsible for some of the failures, but these have escaped detection.

It was shown elsewhere[11] that the immunologic reactions of the serum of patients with Type VII pneumococcus pneumonia differ from those of the other types, including Type V,[9] in that high titers of protective antibodies can be demonstrated for the homologous type during the acute disease. Mouse protective antibodies for Type VII pneumococci may also be demonstrated in normal adults.[11]

The results of treatment with specific antipneumococcus rabbit serums were similar, in general, to those obtained with corresponding horse serums. The number of cases, both these and the ones included in other recent reports[13,15] are too few to draw conclusions concerning the relative merits of the one over the other.

Sulphanilamide was not used in these cases in such a manner as to demonstrate its efficacy as a curative agent. In the present state of our knowledge concerning this or similar drugs, it is best to limit their use, when effective specific agents are available, to those cases in which the conditions are not favorable for the most effective use of the specific agent. These include late bacteremic cases or those with mixed infections or superinfections, and in such cases it is best used to supplement specific serum therapy. It is probably most effective in complicating hemolytic streptococcal infections.

Summary and Conclusions. The experiences with specific serums in 81 cases of Type V and in 9 cases of Type VII pneumococcus pneumonias treated at the Boston City Hospital prior to July 1, 1938, are presented.

Among the 81 Type V cases treated in 1935–38, the death rate was 10% as compared with 41% deaths among 234 non-serum treated cases, which included contemporary cases and those occurring in the 6 years before the introduction of specific serum. Following serum treatment clinical improvement was rapid and complete. Deaths occurred only when specific treatment was undertaken in the face of severe complicating conditions or when it was begun after the fifth day in bacteremic cases. Purulent complications probably developed less frequently after specific treatment.

The death rate among the 79 serum treated Type VII cases was 12% as compared with 29% among 160 earlier and contemporaneous non-serum treated cases. Although the results of serum treated were similar, in general, to those obtained in Type V cases, there was an appreciable number of cases in which the serum did not seem to influence the course of the disease and the cause of these failures was not identified. Type VII cases were more frequently atypical and, because this type is relatively frequent in sputum or in pharyngeal cultures of patients without pneumonia, added caution is required in the choice of proper cases for specific treatment.

The serums used for both these types were highly potent. Un-

toward reactions and serum sickness were relatively infrequent. Concentrated antipneumococcus rabbit serums were used in 11 patients. The data in these cases indicate that the rabbit serums are probably equally as effective as the horse serum preparations. More data are necessary to determine any superiority of the one over the other. Likewise too few cases have been treated with sulphanilamide to evaluate the place of this drug in the treatment of pneumococcus pneumonias of these types.

The authors are indebted to the members of the staffs of the various medical services and of the Mallory Institute of Pathology for their most generous coöperation in this study and to the Lederle Laboratories, Inc., and the Massachusetts Antitoxin and Vaccine Laboratories for the supply of serums and the data concerning them.

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THE PERSONALITY TYPE OF PATIENTS WITH TOXEMIAS OF LATE PREGNANCY.

By Lyle G. McNeile, M.D.,
PROFESSOR OF OBSTETRICS, UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES, CALIF.

AND

Ernest W. Page, M.D.,
BERKELEY, CALIF.

(From the Department of Obstetrics and Gynecology, University of Southern California, and the Los Angeles County Hospital.)

It would seem at the outset that a study of psychic make-up would be totally unrelated to the investigation of a group of diseases which are so obviously on a physical basis. The ultimate solution of the etiology of eclampsia and preëclamptic toxemias, however, must rest upon the accumulation of a multitude of facts. It would be fitting to study eclamptogenic toxemias in relation to

certain other hypertensive states in which there are known differences of personality.

It is widely accepted that there is a constitutional type of woman apparently predisposed to the development of the toxemia syndrome in late pregnancy. Clinical observation[2-4] has shown that women who are shorter, heavier, and stockier than usual, and who, in the authors' experience, often reveal such stigmata of endocrine dysfunctions as hypertrichosis, prognathism, android or masculine type of pelves, and peculiar fat distribution show a higher incidence of late toxemias than the tall, slender, asthenic type.

The cardinal sign of the toxemias of late pregnancy is an elevated blood pressure. While the exact mechanism of this hypertension is not known, we are fairly certain that the immediate mechanical cause is an increased peripheral resistance due probably to a generalized increase in arteriolar tonus. In this respect, it resembles the disease commonly referred to as essential hypertension, which also appears to affect a particular group of individuals. Ayman[1] summarizes the literature regarding the characteristics of these persons afflicted with arteriolar essential hypertension, and in a controlled study determined that they possess a distinct psychic make-up. "Their personality is characterized by increased psychomotor activity. They are dynamic, hyperactive individuals with a large and steady output of energy. They tend to be sensitive and quick-tempered. . . . The hypertensive personality has existed as far back as the subject can remember." It is not to be presumed that such personality types play a rôle in the actual causation of the hypertension, nor that the hypertension alters the personality. Ayman believes that both factors are the result of a common hereditary or physical cause, perhaps endocrine in nature.

The methods used by Ayman were duplicated as closely as possible in the present study in an attempt to answer the following questions: Do women who develop preëclampsia or eclampsia also possess a hypertensive personality? Is there any evidence of a lifelong "autonomic imbalance" as reflected by the mental traits and habits of such women? Could such tests prove of value in differentiating preëclamptic toxemia from essential hypertension in pregnancy?

Clinical Material. The clinical material used in this study is comprised of 148 women, all of whom were bed patients on obstetrical wards. The classification of the hypertensive group used throughout is one which has been developed by one of us in this hospital and used exclusively during the past few years. It is based on the probable origin of the elevated blood pressure rather than on symptoms or on urinary findings which are less constant than hypertension in the late toxemias of pregnancy. Any patient presenting a persistent elevation of blood pressure over 140 systolic or 90 diastolic (on three or more determinations at least 1 hour apart)

was placed in this "hypertensive group." Ninety-seven such patients were carefully studied for several days before establishing the final diagnosis. If the diagnosis was still in doubt at the end of the puerperium, the personality inventory was excluded from the present study.

While it is not the purpose of this report to discuss the diagnosis and classification of the late toxemias, it should be mentioned that the routine investigation of any case included the measurement of the blood pressure at least twice daily; a quantitative estimation of albuminuria daily; a quantitative urinary sediment count when abnormal urinary elements were found; examination of the ocular fundi; determinations of non-protein nitrogen, urea, uric acid, and in doubtful cases the urea clearance, blood sugar and carbon dioxide-combining power; and the response of the blood pressure to physical (cold) and psychic (fright) stimuli in selected cases. Particular attention was paid to the prenatal blood pressure record, the behavior of the blood pressure in previous pregnancies and the family history of hypertension and cardiovascular disease. Such patients were then classified as follows:

GROUP I (46 patients). *Preëclamptic toxemia*, defined as that syndrome appearing in the latter half of pregnancy among women previously normal, characterized by hypertension, albuminuria, and certain subjective symptoms, and which, if progressive, may lead to eclampsia. The cases were actually subdivided into mild, moderate and severe grades, although for the purpose of this study such subdivision was not made.

GROUP II (16 patients). *Chronic vascular-renal disease following known previous preëclamptic or eclamptic toxemias.* This group, often referred to as "recurrent toxemias," warrants segregation for several reasons. It consists only of multiparæ who have records of previous preëclampsia or eclampsia and who show a recurrence of hypertension and albuminuria with succeeding pregnancies. Histologic studies of the kidneys from such cases have revealed a type of permanent glomerular damage quite distinct from the chronic glomerulonephritis which develops apart from pregnancy. Clinically, the hypertension may be out of all proportion to the degree of albuminuria or toxic symptoms.

GROUP III (16 patients). *Eclampsia*, defined as a preëclamptic toxemia with the addition of convulsions or coma or both.

GROUP IV (8 patients). *Hemorrhagic Bright's disease* (chronic glomerulonephritis) complicating pregnancy, but definitely antedating pregnancy. (Combined with Group II for this study.)

GROUP V (11 patients). *Essential (arteriolar) hypertension complicating pregnancy.* In these cases the hypertension usually began before or very early in pregnancy and persisted following the puerperium. There were few, if any, subjective symptoms and rarely more than a trace of albumin (although occasionally the full

syndrome of preëclampsia would suddenly be superimposed upon this basic picture as the patient approached term). The blood pressure showed excessive lability to stimuli. Blood analysis values were all within normal limits. There was frequently a familial history of hypertension. These cases were segregated through careful investigation from Groups I, II and IV.

In addition to the above patients, a group of 51 normal pregnant women were studied under identically the same conditions. Blood pressures were taken with mercury sphygmomanometer and auscultation on admission (before bed rest), during labor and at least once during the puerperium. The patient was excluded as a control if any readings exceeded 140 systolic or 90 diastolic. The only factor entering into the selection of these controls was the age of the patient for it was desired to have the same mean age and age distribution in the control group as in the hypertensive group.

Table 1 gives data regarding the age, parity, prenatal care, height, weight and weight gain with pregnancy for each group.

Method of Present Study. A set of questions identical with those developed by Ayman was used (see list of questions below) and the same method of questioning applied.

TABLE 1.—AGE, PARITY, PRENATAL CARE, HEIGHT, WEIGHT, AND WEIGHT GAIN WITH PREGNANCY OF EACH GROUP STUDIED.

Group.*	No. of cases.	Mean age.	Primiparæ, %.	Average No. mos. prenatal care.	Mean height.	Mean weight (non-pregnant) in lbs.	Mean weight gain with pregnancy.
N	51	26.5	32	3.7	5′4″	120	21
I	46	26.0	60	2.9	5′2″	124	29
III	16	25.0	55	3.6	5′3″	130	32
II and IV	24	34.0	8	3.7	5′5″	143	27
V	11	30.0	10	3.1	5′5″	140	19

* N = Normal pregnancy.
I = Preëclamptic toxemia, all grades.
III = Eclampsia.
II and IV = "Recurrent toxemias" and chronic nephritis in pregnancy.
V = Essential hypertension in pregnancy.

It may be noted upon comparison of the results of this study with that of Ayman that the percentage of positive answers among the control group and the essential hypertension group are, with few exceptions, consistently higher in the present study. Since the evaluation of the patient's personality traits as judged by the answers to these questions varies considerably with different observers, this difference in interpretation may be partially accounted for. It is also apparent that all patients in this series are women whereas about three-fourths of Ayman's patients were men, and this may account for some difference in the subjective evaluation of certain traits. The fact that all had just passed through a period of pregnancy may have unavoidably influenced the answers. It is possible, for example, that women may more readily admit being unusually sensitive, more easily "excited within themselves," more easily embarrassed, or more susceptible to blushing, for it cannot be denied that such traits are often thought to be "feminine weaknesses" and falsely denied by males. For these reasons, the numerical results of the present report are not strictly comparable with those of the preceding study, being consistently higher throughout.

The complete list of questions utilized is as follows:

1. In general, throughout your life, not on any one special occasion and compared with the average person of your own age with whom you have come in contact, have you been of an unusually high-strung or of a calm nature?

2. In general, etc. . . . (as in Question 1) have you been the sort of person who loses his temper quickly (who flies off the handle easily over little things), or has it usually required a good deal to make you lose your temper?

3. In general, etc. . . . have you been the sort of person who, even if you don't show it externally, feel yourself frequently getting all excited over little things?

4. In general, etc. . . . have you been the sort of person whose feelings are unusually easily hurt, who is unusually sensitive, or does it take a great deal to make you feel hurt?

5. As a younger person, did you or do you still blush or flush unusually easily, compared with the average person of your age? Would people "kid you about it"?

6. As a younger person did you, or do you still become unusually easily embarrassed compared with the average person?

7. In general, etc. . . . (as in Question 1) have you been the sort of person who worries unusually easily over little things, or have you tended to pass them over?

8. In general, etc. . . . have you been of an unusually serious nature or of a happy-go-lucky nature?

9. In general, etc. . . . have you been of an unusually forward or unusually shy nature?

10. In general, etc. . . . have you ever had frequent nosebleeds?

11. In general, etc. . . . have your hands or feet tended to become easily cold on slight changes of weather?

12. In general, etc. . . . have you tended to walk at an average pace, slower than the average person, or definitely faster than the average person?

13. In general, etc. . . . have you tended to work at an average pace, slower than the average person, or definitely faster than the average person?

14. In general, etc. . . . have you tended to eat or talk at an average rate, slower than the average person with whom you eat (or talk) or faster than the average person?

15. In general, etc. . . . have you been of average, less than average, or more than average physical activity?

Only definite replies were used. A doubtful response was never counted as a positive answer to that particular question.

Results. The results of the questioning are presented in Table 2. It is readily apparent that the incidence of a familial history of hyper-

tension among Group V (essential hypertension) is three times that of the control group. In Groups II and IV the incidence is also increased, but less than twice, while in the true toxemias of pregnancy (Groups I and III) the differences are hardly significant.

TABLE 2.—PERCENTAGE INCIDENCE OF CERTAIN PERSONALITY CHARACTERISTICS OF EACH GROUP STUDIED, AND THE INCIDENCE OF FAMILIAL HYPERTENSION.

Group.*	Number of cases.	Family history of hypertension (%).	1. Highstrung.	2. Quick-tempered.	3. Easily excited within themselves.	4. Sensitive.	5. Blush easily.	6. Easily embarrassed.	7. Easily worried.	8. Unusually serious.	9. Unusually shy.	10. Frequent epistaxis.	11. Hands or feet easily cold.	12. Fast walker.	13. Fast worker.	14. Fast talker or eater.	15. Unusually active physically.	Average of all positive answers.
N . .	51	24	18	30	28	68	50	40	30	30	52	14	32	36	38	20	56	36
I . .	46	26	35	33	54	63	45	37	48	39	54	6	28	24	22	19	52	38
III . .	16	38	19	44	12	62	50	44	50	50	44	6	31	25	25	19	44	35
II and IV	24	42	16	32	48	64	24	40	40	32	64	8	24	56	48	16	64	38
V . .	11	73	91	36	91	100	45	36	100	73	91	9	63	45	63	27	91	64

* N = Normal pregnancy.
I = Preëclamptic toxemia, all grades.
III = Eclampsia.
II and IV = "Recurrent toxemias" and chronic nephritis in pregnancy.
V = Essential hypertension in pregnancy.

In analyzing the results it is seen that over 90% of the patients in Group V stated that they were highstrung, easily excited within themselves, unusually sensitive, easily worried, unusually shy, or unusually physically active. In no other group did over 68% give positive answers to any one of the 15 questions, and in most instances less than half gave positive replies to the questions to which Group V gave 91 to 100% affirmatives. These differences are so marked that they must be considered significant.

In comparing Groups I, III, II and IV with the control group, it is found that the results of questioning vary rather widely in both directions, as one might anticipate in dealing with such data, but there is no consistently higher trend over normal for any of these groups. This may be illustrated in another way by averaging all of the percentages for each group. Such an average *per se* is meaningless except as a basis for comparison. The figures are shown in the column to the extreme right in Table 2. The average for the control group is 36%; for the preëclamptic group 38%; for eclampsia 35%; for recurrent toxemias and nephritis 38%; and for essential hypertension 64%. Only in the last group is this average significantly altered from the normal.

This would indicate that the women with preëclampsia, eclampsia, or nephritis do not differ in these personality traits from normal pregnant women, while essential hypertension does seem to be associated with a more "hypertensive personality."

Discussion. The statistical data given in Tables 1 and 2 indicate that preëclampsia and eclampsia occur more frequently with first pregnancies (as is well known), while nephritis and essential arteriolar hypertension are manifest most commonly in multiparæ; that the weight gain with pregnancy is greater than normal with the true toxemias, and normal or below normal with essential hypertension; that women with true pregnancy toxemias or nephritis have essentially the same personality traits as the normal group, and show no special familial diathesis for hypertension, while women whose pregnancy is complicated by essential hypertension give a family history of hypertension in three-fourths of the cases, and show a definite tendency to increased psycho-motor activity.

It should be emphasized that any differences shown between the various groups are not considered to be of any etiologic importance. The results suggest the possibility, however, that there is some relationship between the nervous system and the mechanism of hypertension in essential hypertension which is not present in the toxemias of late pregnancy.

The differential diagnosis among women showing hypertension in late pregnancy is difficult and at times impossible. No single sign or symptom can be relied upon to classify such cases; nevertheless such classification is highly desirable from the standpoint of prognosis, treatment, and academic research. In the authors' opinion, the classification briefly outlined above is as close to an etiologic grouping as our present knowledge allows. The differences in the personality types of the individuals as demonstrated in the present study, and the differences in the constitutional types as demonstrated so well by other writers[4] should be utilized along with all the other findings of the history and examination in arriving at the proper classification.

Summary and Conclusions. 1. A method used by a previous worker in the study of non-pregnant individuals with essential hypertension has been utilized to study the personality types of women with normal pregnancies, and with pregnancies complicated by preëclamptic toxemia, eclampsia, glomerulonephritis, or essential hypertension.

2. The results indicate that only those women with essential arteriolar hypertension (as a group) differ significantly from the normal in having personalities characterized by an increased psychomotor activity.

3. Further correlations are shown between the diagnosis and the age parity, height, weight gain with pregnancy and family history.

A classification based on the probable origin of the hypertension is suggested for use.

4. The relationship between the hypertensive personality and the late toxemias of pregnancy with its value in differential diagnosis is discussed.

The writers wish to express their thanks to Drs. L. L. Emmons and H. A. Tanton for their assistance in the compilation of data.

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BOOK REVIEWS AND NOTICES

PRACTICAL OTOLOGY. By MORRIS LEVINE, M.D., F.I.C.S., Clinical Professor of Oto-laryngology, New York Post-Graduate Medical School, Columbia University; Attending Oto-laryngologist, New York Post-Graduate Hospital. Pp. 416; 146 engravings and 3 colored plates. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $5.50.

THIS treatise on otology is so concise, practical and clearly written that it can unreservedly be recommended to the undergraduate, the general practitioner and the postgraduate student. It is especially gratifying to this Reviewer to find the chapter on anatomy adorned with adequate and instructive illustrations, the absence of which has been glaringly conspicuous in many recent text books. The description of special functional examination of the hearing and equilibratory apparatus is explicit and instructive. General therapeutic measures in otology are treated in sufficient detail to guide the clinician in their practical application. The importance of allergy in diseases of the ear is outlined with clarity and excellent judgment.

A minimum of text achieves a clear presentation of symptomatology, differential diagnosis and the rationale of therapeutics while the surgical aspects of otology are fully considered and well illustrated. This volume very nearly approaches the ideal in a small textbook on otology.

H. S.

THE PRINCIPLES AND PRACTICE OF MEDICINE. Designed for the Use of Practitioners and Students of Medicine. Originally written by The Late SIR WILLIAM OSLER, BART., M.D., F.R.C.P., F.R.S., formerly Regius Professor of Medicine, Oxford University; Professor of Medicine, Johns Hopkins University, Baltimore, etc. Revised by HENRY A. CHRISTIAN, M.D., LL.D., S.D., F.R.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard University; Physician in Chief, Peter Bent Brigham Hospital, Boston. (9th, 10th, 11th and 12th editions were revised by THOMAS MCCRAE, M.D., F.R.C.P., Formerly Professor of Medicine, Jefferson Medical College, Philadelphia.) Pp. 1424; illustrated. Thirteenth Edition. New York: D. Appleton-Century Company, 1938. Price, $9.00.

IN this latest edition, this textbook, so long a favorite, has been conspicuously modernized by its new editor. The improved typography is larger, requiring more pages, but facilitating reading and with better selection of headings. New concepts are reflected in changes in arrangement of the diseases, notably of the infections. In the introductory remarks that open certain sections, aspects of pathologic physiology are discussed.

Etiology and treatment of important infections, notably lobar pneumonia and streptococcal diseases have been revised. The section on anemia has been in part rewritten. The section on Bright's disease, entirely rewritten, reflects the editor's preference for the simplest clinical classification and one that will appeal to many clinicians; the new paragraphs on uremia are not perhaps an improvement. The editor's method of presenting prognosis in heart disease in general and symptoms and treatment of cardiac decompensation in a special section is commendable.

This revision effectively prolongs the usefulness of a standard work.

J. A.

CHIRURGIE DER LUNGEN UND DES BRUSTFELLES. (Band 26 of Medizinische Praxis. Sammlung für Ärztliche Fortbildung, Herausgegeben von Prof. Dr. L. R. Grote, Prof. Dr. A. Fromme and Prof. Dr. K. Warnekros.) By DR. ALFRED BRUNNER, Chirurg. Chefarzt am Kantonsspital St. Gallen; Früher Privatdozent für Chirurgie an der Universität München. Pp. 282; 112 illustrations. Dresden: Theodor Steinkopff, 1938. Price, Paper, Rm. 22.50; Bound, Rm. 24.00.

THIS little volume is one of a series of practical monographs on special subjects. The author hopes that it will bring together the many advances which have been made in the field of pulmonary surgery in the last few years. The surgery of the heart and mediastinum is not included. There are 10 chapters, a short bibliography, an author and a subject index. There are short chapters on lung abscess, gangrene, bronchiectasis and benign and malignant tumors. Nearly one-half of the monograph is concerned with a discussion of management of tuberculosis by collapse therapy. The management of acute and chronic empyema and tuberculous empyema is reviewed. While it should not be used as a textbook of thoracic surgery by the beginner, it will provide a bird's-eye view of the subject and be useful for reference. The majority of the references are continental and the Reviewer is surprised that no mention is made of the work of Graham or Churchill in the entire volume. Surely Graham's work in empyema and malignant disease, and Churchill's in bronchiectasis are more important than much which has been reviewed. I. R.

UEBER DIE BEZIEHUNGEN DER QUALITÄT DES NAHRUNGSEIWEISSES ZUM ABLAUF DES BETRIEBSSTOFFWECHELS. Heft 3. Schriftenreihe zur Schweizerischen Medizinischen Wochenschrift. By ADOLF BICKEL, Professor of Pathological Physiology in the Friedrich-Wilhelm University, Berlin. Pp. 100. Basel: Benno Schwabe & Co., 1938. Price, Fr. 10.

THIS short monograph contains a group of related papers, presenting the experimental data accumulated in the author's laboratory. As the title indicates, the purpose of the work was to study the effect of the quality of the food proteins upon "working metabolism" as distinguished from "structural metabolism." The latter term refers to metabolic processes associated with growth and regeneration, while the former term refers to metabolic processes, which may be measured by the daily drain of metabolites, C and N compounds, in the urine. The experimental work was largely upon rats, although data upon man is also presented. Many tables give figures for C and N outputs. D. D.

MENINGIOMAS. Their Classification, Regional Behaviour, Life History, and Surgical End Results. By HARVEY CUSHING, M.D., Sometime Associate Professor of Surgery, Johns Hopkins University; Moseley Professor of Surgery, Harvard University, and Surgeon-in-chief, Peter Bent Brigham Hospital, Boston, etc. With the Collaboration of LOUISE EISENHARDT, M.D., Assistant Professor of Pathology, Yale University School of Medicine; Formerly Associate in Surgery, Peter Bent Brigham Hospital, Boston. Pp. 785; 685 illustrations. Springfield, Ill.: Charles C Thomas, 1938. Price, $15.00.

THIS work by two well-known investigators of neuro-pathological problems may be considered a sequel to the senior author's monograph on "Tumors of Nervous Acusticus," published in 1917. It is based upon a detailed analysis of 313 cases of meningiomas, all of them histologically verified. The meningiomas are broadly considered from the point of view of internist, neurologist, surgeon, and pathologist. Case histories contain-

ing all the necessary data are given, as well as operative procedures. The probable etiologic factors, the symptomatology, and the steps leading to diagnosis, the end results and pathologic aspects are clearly discussed. The many excellent illustrations include not only photographs of specimens but of patients as well. A well selected bibliography of over 500 titles is appended. The monograph is written in the lucid style that characterizes all the contributions with which Dr. Cushing's name is associated. Here is an altogether worth-while book, and a monument to the painstaking care and industry of an illustrious surgeon. B. L.

ESSENTIALS OF OBSTETRICAL AND GYNECOLOGICAL PATHOLOGY. With Clinical Correlation. By MARION DOUGLASS, M.D., F.A.C.S., Assistant Professor of Gynecology, Western Reserve University, and ROBERT L. FAULKNER, M.D., Senior Clinical Instructor in Gynecology, Western Reserve University. Pp. 187; 148 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, $4.75.

IN this book are discussed briefly and from a clinical point of view the normal structures and the more important pathologic processes of the female sex organs. The book is accompanied by many good illustrations, most of them photographs illustrating gross and microscopic pathologic material. There are chapters on the vulva and vagina, the cervix, endometrium, the myomatous tumors of the uterus, endometriosis, the Fallopian tubes, ovary, and the pathologic conditions incident to gestation.

The book should prove of value to the graduate and undergraduate students of obstetrics and gynecology as a well written, clear, and brief text on the pathology of the female generative organs. B. L.

THE CHEMISTRY OF THE AMINO ACIDS AND PROTEINS. Edited by CARL L. A. SCHMIDT, M.S., PH.D., Professor of Biochemistry, University of California. Pp. 1031; 259 illustrations and 144 tables. Springfield, Ill.: Charles C Thomas, 1938. Price, $7.50.

As it is impossible to review a book of this magnitude in the small space allotted, the chapter headings with their authors will be sufficient to give an idea of the scope and thoroughness of this work.

Part I. Chemical Statics of Amino Acids and Proteins: Historical (C. L. A. Schmidt); The Constitution and Synthesis of the Amino Acids (M. S. Dunn); *a*, The Isolation of the Amino Acids from Proteins (H. O. Calvery); *b*, The Preparation of Amino Acids and Proteins (C. L. A. Schmidt); Methods of Analysis and Reactions of the Amino Acids and Proteins (H. O. Calvery); The Relation of the Amino Acids to Products of Biochemical Importance (C. L. A. Schmidt); Peptides, Peptidases and Diketopiperazines (J. P. Greenstein); The Chemical Constitution of the Proteins (R. J. Block); Certain Chemical and Physical Characteristics of the Proteins (15 sections) (M. L. Anson, Evert Gorter, A. A. Vander Dussen and L. Maaskant, D. M. Greenberg, C. L. A. Schmidt, J. T. Edsall); Optical Properties of Amino Acids and Proteins (D. M. Greenberg).

Part II. Chemical Dynamics of Amino Acid and Proteins. Amphoteric Properties of Amino Acid and Proteins (D. M. Hitchcock); Electrochemistry of Amino Acids and Proteins (C. L. A. Schmidt); Combination of Amino Acids and Proteins with Acids, Bases, Heavy Metals and Other Compounds (C. L. A. Schmidt); Membrane Equilibria (D. M. Greenberg); Some Thermodynamical Considerations of Amino Acids, Peptides, and Related Substances (H. Borsook and H. M. Huffman); Dipolar Ionic Structure and Solubility of Amino Acids, Peptides and Proteins (J. T.

Edsall); Relation of Proteins to Immunity (M. Heidelberger); The Rôle of Proteins in Nutrition (R. W. Jackson).

Although there are some errors and some of the more recent work is not included, this volume covers protein chemistry very completely. It is also very well edited as there is practically no repetition of material in spite of its being written by a number of authors. J. J.

DER ZYKLUS DER FRAU. Reform Des Ehelebens. By DR. JULES SAMUELS, Chirurg-Frauenarzt, Leiter der Einrichtung für Kurzwellentherapie, Amsterdam. Pp. 175; 43 illustrations (some in colors). Haag: G. Naeff, 1938. Price not given.

WRITTEN for lay consumption, this book offers a new method of determining the time of ovulation, presence of pregnancy and the problems of menstruation with both normal and abnormal women.

The proposed simple examination by which these conditions may be determined is made possible by the use of a new instrument, the "Cycloscope." This consists of a spectroscope and a powerful lamp mounted on a stand with an examining platform upon which the patient's hand is to be placed. This test is made by examining the delicate tissue between the thumb and forefinger with relation to the spectroscopic changes in the oxyhemoglobin content of the blood as it passes this point. The reduction time figured by changes in the spectroscopic analysis of the blood viewed through the instrument is believed to bear a very definite relation to the hormone content of the blood of the woman.

The book is illustrated with colored plates indicating changes in the spectroscopic readings. Cyclograms show the relationship of menstruation and other objective changes to the recorded reduction times. Samuels demonstrates by such graphs that more than one ovulation per cycle is likely, and frequently happens in many women, and seeks thereby to disprove the theory of Knaus-Ogino. He states that the first and second ovulations are usually from 5 to 7 days apart. P. W.

MANUAL OF VETERINARY BACTERIOLOGY. By RAYMOND A. KELSER, D.V.M., A.M., PH.D., Lieut. Colonel, Veterinary Corps, United States Army; Chief, Veterinary Division, Surgeon General's Office, War Department, Washington, D. C., etc. Pp. 640; 93 illustrations and 11 tables. Third edition, thoroughly revised. Baltimore: The Williams & Wilkins Company, 1938. Price, $6.00.

THE third revised edition is 90 pages longer than the previous one and contains additional valuable information in most of its parts. Advancements in the field of immunology have been taken into account and the author presents a fuller discussion of virulence of bacteria and of dissociation.

Bergey's classification of bacteria is essentially adhered to, including the changes of the 1934 edition. In the section dealing with pathogenic organisms new information is incorporated, namely, the bacteriology of *vibrio jejuni, hemophilus influenzæ (suis), hemophilus canis, corynebacterium equi* and a more detailed discussion of the streptococcus group. The section on pathogenic fungi is enriched by the description of *trypanosoma cruzi*, the cause of Chagas' disease. More recently established virus diseases as swine influenza, fowl tumors, rabbit fibroma, rabbit papilloma and equine infectious abortion are included.

The book contains very useful information for the student and laboratory worker in animal bacteriology and the author is to be congratulated for bringing it up to date in the present edition. E. S.

THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE. Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. Vol. IX. Mumps to Pneumothorax, Spontaneous. Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, G. GREY TURNER, JAMES YOUNG, SIR LEONARD ROGERS, F.M.R. WALSHE. Pp. 805; 117 illustrations and 10 plates (1 in color). London: Butterworth & Co. Publishers, Ltd., 1938. Price, $12.00.

As usual in this Encyclopedia, a number of well-known names appear in the list of authors. Among the subjects treated at greater length are Nephritis and Nephrosis, Neuritis, Diseases of the Oesophagus, Ovary, Parathyroid, Placenta, Peptic Ulcer, Plague, and Lobar Pneumonia. Even these subjects, however, and even in such an extensive encyclopedia as this one is, cannot be expected to receive the kind of treatment that they would receive in a monograph, or System of Medicine. E. K.

CARBON MONOXIDE ASPHYXIA. By CECIL K. DRINKER, M.D., D.Sc., Professor of Physiology and Dean, School of Public Health, Harvard University. Pp. 276; 40 illustrations, and 21 tables. London: Oxford University Press, 1938. Price, $4.50.

"THIS book is written primarily for men who have practical concern with the problems of carbon monoxide asphyxia" says the author in his preface. It will serve this purpose admirably for it is clearly written, and most of the points made are so expressed as to be intelligible to those with little scientific background. In spite of this commendable simplicity, it gives an excellent account of the subject from the professional viewpoint and there will be few physiologists who will not find it a valuable source of information. The whole account is well illustrated by detailed reports of individual reactions to carbon monoxide poisoning and includes some of the graphic descriptions given by the late Professor J. S. Haldane of his own historical experiments. An interesting historical account is also given of the various means of artificial respiration. The bibliography contains 335 references with titles. There can be little question but that this book will prove extremely useful alike to laymen, clinicians and physiologists.

H. B.

PRACTICAL PROCEDURES. (The Practitioner Handbooks.) Edited by SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., F.R.C.P., and ALAN A. MONCRIEFF, M.D., F.R.C.P. With a Preface by SIR DAVID WILKIE, O.B.E., M.D., M.CH., F.R.C.S., F.A.C.S., F.R.S.E. Pp. 293; 66 illustrations. London: Eyre and Spottiswoode (Publishers), Ltd., 1938. Price, 10s. 6d.

THIS is a handbook intended to serve the general practitioner as a practical guide to clinical procedures. Eighteen authors have contributed chapters on such topics as plaster-of-Paris technique; administration of fluids; indications and technique for blood transfusions; pleural aspiration; the use of two- and three-way syringes; catheterization; circumcision in children; minor surgical affections of the skin; local anesthesia; lumbar puncture in general practice; syringing the ear. The advantage of such a book is that it includes material which would otherwise have to be looked for in many textbooks. The subject matter is concise and practical, and the illustrations are adequate. R. K.

THE NEW-BORN INFANT. A Manual of Obstetrical Pediatrics. By EMERSON L. STONE, M.D., Associate Clinical Professor of Obstetrics and Gynecology, School of Medicine, Yale University; Attending Obstetrician and Gynecologist to the New Haven Hospital. Pp. 291. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $3.00.

THE second edition of this little treatise on the care of newly born infants shows an enlargement of approximately 100 pages. It is in consequence up to date in most respects and more valuable than the first to the practitioner.

The author reiterates his belief that the "new-born period" is neglected alike by obstetrician and pediatrician. It is the opinion of this Reviewer that progress in this field has come through the pediatric study of the newborn. In most good hospitals these cases are cared for by pediatricians and have been for many years. In consequence of the authors' obstetrical training those sections of the book which deal with the immediate or emergency case of the infant and with the accidents incident to delivery are handled most capably. Such matters as resuscitation of the infant and, intracranial hemorrhage are completely and excellently covered.

One feels that the introduction of tables of data, more references, and a few well chosen illustrations would enhance the value of the book. In the main, it serves as an introduction to the subject rather than as a complete treatise and is of great value to the beginning student.

E. T., JR.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. XI. Tagung. Zu Bad Nauheim vom 26.-27. Marz 1938. Herausgegeben von Prof. DR. EB. KOCH, Bad Nauheim. Pp. 430; illustrated. Leipzig: Theodor Steinkopff, 1938. Price, Rm. 11.25.

THE *Haupthema* of this session was Circulatory Collapse to which more than 20 articles in this volume are devoted. Burns, hemorrhage, surgery, histamine, child birth, lung emboli, all are discussed and various opinions maintained. There are also 16 papers on miscellaneous subjects. One does not recognize many familiar names among the authors; the long Autoren-Register is a useful list referring to all authors mentioned in the text.

E. K.

DRUG ADDICTS ARE HUMAN BEINGS. The Story of our Billion-Dollar Drug Racket, How We Created It and How We Can Wipe It Out. By HENRY SMITH WILLIAMS, M.D., B.Sc., LL.D. Pp. 273; illustrated. Washington, D. C.: Shaw Publishing Company, 1938. Price, $2.50.

IN 1914, the Harrison Narcotics Law was enacted, the intent of which was to have physicians sole distributors of narcotic drugs; since then, the Supreme Court has ruled that addiction is a disease; furthermore, in the review of a narcotic case in 1935, the Supreme Court declared the Federal Government has no control over the practice of a profession. Nevertheless, the Narcotic Code has often denied addicts the right of procuring narcotic preparations from physicians. By reason of this illegal ruling, many addicts have had recourse to drug peddlers, to whom they sometimes paid an exorbitant price for a greatly adulterated product. It is estimated we have at least 500,000 addicts, three-fourths of whom are said to be engaged in gainful pursuits. In Los Angeles, a Narcotic Clinic was established for afflicted addicts. And, "though monumentally successful during the three years of its operation, fell before the organized attack of the Federal coadjutors of the billion-dollar racket," despite their illegal and unconstitutional actions. Approximately 25,000 physicians have been prosecuted, with fines as high as $10,000 and sentences as much as ten

years, "after having committed no crime!" It is said that the remedy for "Our Billion-Dollar Racket" is not a new law, but recognition of the rulings of the Supreme Court, by the lower courts. Justice Roberts has stated: "Federal law cannot regulate the practice of a profession." However, present indications are that we shall have Federal control. One wonders at the rapid spread of the narcotic vice, with so much of peddlers' supply an inferior product, at extortion prices. N. Y.

MODERN ANÆSTHETIC PRACTICE. (The Practitioner Handbooks.) Edited by SIR HUMPHRY ROLLESTON, BT. G.C.V.O., K.C.B., M.D., F.R.C.P., and ALAN A. MONCRIEFF, M.D., F.R.C.P. Pp. 231; illustrated. London: Eyre & Spottiswoode (Publishers) Ltd., 1938. Price 10s. 6d.

THIS book is not a contribution to the scientific advancement of anesthesia and in some parts falls distinctly short of modern anesthetic practice as taught by the best anesthetists in this country. The chapter that deals with the theoretical aspects consists of many statements from the literature without due regard to their source. Emphasis is placed on the technical methods of anesthesia in England and this is quite properly stressed in this book. However, even in a practical treatise, the fundamental physiological principles should be given more attention than they have been in most of the several chapters of this book. It is therefore not suitable for a textbook and only certain chapters are worthy for use as references. No doubt it fills the purpose for which it was written, namely as an aid to the general practitioner in England; but because of the differences in anesthetic training it does not have the same value in the United States. L. F.

SUBACUTE AND CHRONIC PERICARDIAL AND MYOCARDIAL LESIONS DUE TO NON-PENETRATING TRAUMATIC INJURIES. A Clinical Study. By ERIK WARBURG, M.D. With a Short Biography of Oluff Borch (Olaus Borrichius) by TORBEN GEILL, M.D. Pp. 147; 18 illustrations. Copenhagen: Levin & Munksgaard, 1938. Price, Kr. 14.00. (London: Humphrey Milford; Oxford University Press, Price, 12s. 6d.)

DESIRING more detailed knowledge about cardiac disease resulting from non-penetrating trauma, the author has collected from the literature and analyzed 184 examples of pericardial and myocardial lesions from this cause, and added 12 "new" cases, of which he gives detailed records. He found disorders ranging from transient electrocardiographic changes and arrhythmias to rupture and sudden death and notes that many developed congestive heart failure. He believes that it is a much commoner cause of heart disease than is generally suspected. The 2 first cases reported—by Olaus Borrichius and Stephen Blankaard—are reproduced in English and in facsimile together, with a biography of Borrichius. E. K.

PRACTICAL MICROBIOLOGY AND PUBLIC HEALTH. For Students of Medicine, Public Health, and General Bacteriology. By WILLIAM BARNARD SHARP, S.M., M.D., PH.D., Professor of Bacteriology and Preventive Medicine in the Medical Department of the University of Texas; Visiting Bacteriologist of John Sealy Hospital, Galveston, etc. Pp. 492; 125 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, $4.50.

THIS work is an effort to include in one "laboratory" manual all of the subjects covered in a course of training for public health workers. The book embraces as laboratory exercises general bacteriology, vehicles of infection, clinical bacteriology and mycology, immunology and animal para-

sitology. In addition are included directions for field surveys and the handling of office problems of administration.

While as a manual of directions for use of students taking a course covering the included subjects it would no doubt be very helpful, the Reviewer doubts the wisdom of attempting to cover so much ground in one manual. For the student it would be better to have the subject matter split up into three or more smaller manuals. To keep a laboratory manual up to date and not have it too static, it is better to issue it as loose leafed mimeographed material easily revisable from year to year.

In no way can this book be regarded as a text book. Even as a manual it seems to the Reviewer to be inadequate, as the effort to simplify and condense has resulted in inadequacy and incompleteness of directions, lack of clear explanations of procedures and results, and in the omission of various newer methods. H. S.

SPINAL ANESTHESIA. By LOUIS H. MAXSON, A.B., M.D., Practising Specialist in Anesthetics; former Chief Anesthetist, Harborview (King County) Hospital, Seattle, Wash. Foreword by W. WAYNE BABCOCK, M.D., LL.D., F.A.C.S., Professor of Surgery, Temple University School of Medicine. Pp. 409; 69 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, $6.50.

THE author has reviewed the subject of spinal anesthesia from the physical, anatomic and physiologic viewpoint according to the literature to date. He has added to this his personal experience and discussed many of the points over which controversy still exists.

The physical aspects of spinal anesthesia are well presented. While the claims for this type of anesthesia are, as the author states, more conservative than in some texts of the past, they are those of an enthusiast for spinal anesthesia. The book has a subject index and complete bibliography. It is a good text for reference purposes and will prove helpful to those who have not had the opportunity to follow the literature on the subject. I. T.

NEW BOOKS.

Trauma and Internal Disease. A Basis for Medical and Legal Evaluation of the Etiology, Pathology, Clinical Processes, Following Injury. By FRANK W. SPICER, A.B., M.D., F.A.C.P. Pp. 593; 43 illustrations. Philadelphia: J. B. Lippincott Company, 1939. Price, $7.00.

Textbook of Neuro-anatomy and the Sense Organs. By O. LARSELL, PH.D., Professor of Anatomy, University of Oregon Medical School, Portland. Pp. 343; 232 illustrations. New York: D. Appleton-Century Company, Inc., 1939. Price, $6.00.

Out of the Running. By G. GERTRUDE HOOPES. With a Foreword by EDGAR A. DOLL, PH.D., Director of the Department of Research, The Training School at Vineland, New Jersey, and with Clinical Notes by WINTHROP M. PHELPS, M.D., Director of the Children's Rehabilitation Institute, Inc., Baltimore. Pp. 158; illustrated. Springfield, Ill.: Charles C Thomas, 1939. Price, $2.00.

Life's Beginning on the Earth. By R. BEUTNER, M.D., PH.D., Professor of Pharmacology at the Hahnemann Medical College and Hospital of Philadelphia. Pp. 222; 80 illustrations. Baltimore: The Williams & Wilkins Company, 1938. Price, $3.00.

Medizin und Kultur. Gesammelte Aufsätze. By PAUL DIEPGEN. Zu seinem 60. Geburtstag am 24. November, 1938. Herausgegeben von W. ARLETT, E. HEISCHKEL, J. SCHUSTER. Pp. 309. Stuttgart: Ferdinand Enke, 1938. Price, Paper, Rm. 21, Bound, Rm. 22.80.

Surgical Pathology of the Diseases of the Mouth and Jaws. By ARTHUR E. HERTZLER, M.D., Surgeon to the Agnes Hertzler Memorial Hospital, Halstead, Kansas; Professor of Surgery, University of Kansas. Pp. 248; 206 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, $5.00.

Medicine in Modern Society. By DAVID RIESMAN. Pp. 226; Princeton: Princeton University Press, 1938. Price, $2.50.

The Medical Clinics of North America, Vol. 23, No. 1 (Chicago Number, January, 1939). Pp. 271; 23 illustrations. Philadelphia: W. B. Saunders Company, 1939.

The Symposium on the Gall Bladder—10 contributors—is chiefly devoted to the newer aspects of diagnosis and treatment of this clinically important organ. The 15 other papers by Chicago doctors cover a wide range such as Hamburger on Bradycardia, Coulter on Diathermy, Bernstein on Allergy, and W. O. Thompson on the Hypothyroid State.

The Medical Press and Circular, 1839–1939. A Hundred Years in the Life of a Medical Journal. By ROBERT J. ROWLETTE, M.D., F.R.C.P.I. Pp. 127; illustrated. London: The Medical Press and Circular, 1939. (No price given.)

The Medical Press and Circular, founded in Dublin by Dr. Arthur Jacob in January, 1839, under the title of the Dublin Medical Press, celebrates its Centenary with a history of the journal and its development, together with an interesting account of the medical history of the times. In 1866 it combined with the Medical Circular, a London periodical founded in 1852. This journal had an eventful career: its more or less continuous warfare with Wakley of the Lancet and its long series of illustrated biographies were conspicuous. The combined journal has continued to occupy a useful place in English medical literature. The volume is artistically produced; its 10 plates include portraits of the early editors and reproductions of the various title pages.

Cronologia, diferenciación, matricula y distribución geografica de las sociedades de ciencias médicas. By ENRIQUE SPARN, Secretario de la Academia Nacional de Ciencias. Pp. 153; illustrated. Cordoba: Universidad Nacional de Corboda, 1938. (No price given.)

In the Preface it is stated that this is the only monograph of its kind in print. In five parts cover: 1, a list of societies in order of their date of foundation; 2, their general nature; 3, their size; 4, their geographical distribution; and 5, the largest section, their division into 28 different classes. Though far from being exhaustive, this should be a useful reference book for those wanting information on the subject.

The Proceedings of The Charaka Club, Vol. IX. Pp. 204; illustrated. New York: RICHARD R. SMITH for the Charaka Club, 1938.

Principles of Hematology. By RUSSELL L. HADEN, M.A., M.D., Chief of the Medical Division of the Cleveland Clinic; Formerly Professor of Experimental Medicine in the University of Kansas School of Medicine, Kansas City, Kansas. Pp. 348; 155 illustrations and 1 colored plate. Philadelphia: Lea & Febiger, 1939. Price, $4.50.

Del Carcinoma Primitivo Broncopulmonar. By NICETO S. LÓIZAGA, Profesor adjunto de Patologia Médica, Docente libre de Clinica de Enfermedades Infecciosas de la Facultad de Ciencias Médicas de Buenos Aires. Pp. 221; illustrated. Buenos Aires: Libreria y Editorial "El Ateneo," 1938.

Based on 46 original cases of primary carcinoma of lung, and reports from the literature, the authors consider the subject from the point of incidence, etiology and pathogenesis, pathology, symptoms, diagnosis, prognosis and treatment.

A Manual of Fractures and Dislocations. By BARBARA BARTLETT STIMSON, A.B., M.D., MED. SC.D., F.A.C.S., Associate in Surgery in the College of Physicians and Surgeons, Columbia University, New York City; Assistant Attending Surgeon to the Presbyterian Hospital, New York City. Pp. 214; 95 illustrations. Philadelphia: Lea & Febiger, 1939. Price, $2.75.

The British Encyclopædia of Medical Practice. Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. Vol. 10. Poisons Legislation to Rosacea. Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London, with the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., and F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 731; 79 illustrations and 11 plates (4 in color). London: Butterworth & Co. (Publishers), Ltd., 1938. Price, $12.00 per volume.

The present volume covers from Poisons Legislation through Rosacea, the most extensive articles being, as one might expect, on Pregnancy and the Psychoses. Perusal, though admittedly brief, indicates that the high standard of previous volumes has been maintained.

NEW EDITIONS.

Immunity Principles and Application in Medicine and Public Health. An Exposition of the Biological Phenomena of Infection and Recovery of the Animal Body from Infectious Disease, with Consideration of the Application of the Principles of Immunity to Diagnosis, Treatment, and Prophylaxis and Their Usefulness in the Control of Epidemics. By HANS ZINSSER, M.D., Professor of Bacteriology and Immunology, Harvard Medical School, JOHN F. ENDERS, PH.D., Assistant Professor of Bacteriology and Immunology, Harvard Medical School, and LEROY D. FOTHERGILL, M.D., Assistant Professor of Bacteriology and Immunology and Associate in Pediatrics, Harvard Medical School. Pp. 801. Fifth Edition of "Resistance to Infectious Diseases." New York: The Macmillan Company, 1939. Price, $6.50.

Fundamentals of Experimental Pharmacology. By TORALD H. SOLLMANN, M.D., Sc.D., Professor of Pharmacology and Materia Medica, and Dean of the School of Medicine, Western Reserve University, Cleveland, etc., and PAUL J. HANZLIK, A.M., M.D., Professor of Pharmacology, Stanford University School of Medicine, San Francisco, etc. Pp. 307; 36 illustrations. Second Edition. San Francisco: J. W. Stacey, Inc., 1939. Price, $4.25.

Infections of the Hand. A Guide to the Surgical Treatment of Acute and Chronic Suppurative Processes in the Fingers, Hand and Forearm. By ALLEN B. KANAVEL, M.D., Sc.D., Late Professor of Surgery, Northwestern University Medical School, Chicago; Attending Surgeon, Wesley Memorial and Passavant Memorial Hospitals, Chicago. Pp. 503; 229 illustrations (many in color) and 1 colored plate. Seventh Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, $6.00.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF
W. L. HOLMAN, M.D., C.M.,
PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,
AND
G. LYMAN DUFF, M.A., M.D., PH.D.,
ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

THE BOVINE TUBERCLE BACILLUS IN HUMAN TUBERCULOSIS.

ROBERT KOCH, at the International Congress on Tuberculosis in London in 1901, grudgingly acknowledged the existence of the bovine type of tubercle bacillus, but regarded it as of no real significance in human infection. He modified this extreme view in Washington, in 1908, but since pulmonary tuberculosis constitutes by far the greatest proportion of tuberculous infection in man, and believing it was invariably caused by the human type, he still maintained that bovine tuberculosis was of slight significance in the human disease.

The purpose of this review is to indicate the increasing evidence for the importance of the bovine tubercle bacillus not only in extrapulmonary tuberculosis, but also its frequency in tuberculosis of the lung which was until recently regarded as almost non-existent.

In the general problem of the control of tuberculosis the infections with the bovine type of bacillus are fully preventable. They depend upon the eradication of the disease in cattle or the control of the milk supply by pasteurization. In those countries where milk is boiled before consumption bovine infection in man is relatively infrequent.

Isolation. The inoculation of the guinea pig has been until recently practically the only method used for the primary isolation of mammalian tubercle bacilli. It is important to realize that these bacteria are not always easy to grow, particularly when dealing with the bovine type from human sources, and the growing tendency to substitute cultural for animal inoculation methods must unquestionably result in failure to isolate bovine strains in certain instances. Animal inoculation and cultural methods were used: by Griffith[49c] in studying strains from skin lesions; by Gosling and Montanus[46] in a study of 34 specimens of cerebrospinal fluid in suspected tuberculous meningitis, and tubercle bacilli were obtained 25 times in culture; by Griffith[49f] who reserved the animal test for material showing a paucity of organisms, or in those secondarily infected; by Ledermann[69a] who reported better results by the use of cultural methods; by Lange[66b] in his studies of bovine phthisis

(tuberculosis of lung in man caused by the bovine type); by Stadnichenko and Sweany[122] in a study of pulmonary tuberculosis. They isolated human tubercle bacilli from 69 cases out of 200 studied; of these, 33 were positive on both culture and guinea pig inoculation; 33 in guinea pig inoculation, and negative in culture; and 3 were positive in culture but negative in guinea pig inoculation; by Feldman[41] who found in 27 specimens from various human sources 24 positive on guinea pig inoculation while 23 were positive in culture; and in a study of 19 specimens of bovine material (from bovine sources) 18 strains were recovered on guinea pig inoculation and 16 by culture; by Saenz, Le Mée and Costil[114] who stated that cultural methods suffice for material in which 4 tubercle bacilli can be seen in each high power field; by Lester[71] who reserved guinea pig inoculation for all material from children under 5 years of age, the age group in which the highest incidence of bovine infection is known to occur; by Mündel and Strempel[83] in all cases of suspected bovine tuberculosis; by Blacklock and Griffin[13] in a comprehensive study of tuberculous meningitis in children, and they emphasized that cultural methods were positive only in 50% of the bovine strains recovered from the cerebrospinal fluid; by Piasecka-Zeyland[101] in his general survey studies in Poland; and Lange[66c] in the isolation of the tubercle bacillus from the sputum in a survey study of bovine phthisis, while Ruys[111] preferred guinea pig inoculation to cultural methods in survey work upon the incidence of bovine tuberculosis in Holland.

Jensen and Frimodt-Moller[60] have since 1934 used cultural methods exclusively and were successful in culturing many bovine strains. Rocher and Laporte[108] and Saenz[112b] used cultural methods extensively but not solely. Green[48] in routine work, in an analysis of results obtained in a study of 1306 specimens by means of culture and guinea pig inoculation, concluded that cultural methods are practicable, but that animal inoculation gave as a rule a higher number of positives. No mention is made of the types of tubercle bacilli recovered.

The method of Negre, Valtis, Van Deines and Beerens,[90] which according to the authors permits the isolation of the tubercle bacillus through guinea pig inoculation in some cases where the ordinary inoculation is negative, consists in treating the inoculated animals with an acetone extract of the Koch bacillus. Strains of acid-fast bacilli of extraordinary biologic qualities were thus recovered which are designated as probably "intermediates." Valtis and van Deinse[131] believed that by this method filtrable forms of tubercle bacilli are developed, and that they could differentiate these filtrable forms of tubercle bacilli from the acid-fast forms occasionally found in the glands of normal guinea pigs (found in 9 uninoculated animals). This work has not been confirmed, and will need a great deal of controlled work before it can be accepted as valid.

Cultivation. In growing tubercle bacilli, particularly from small plantings, special conditions must be maintained and special media used. In cultivating the human type glycerin, first used by Nocard and Roux,[91] should be added to media containing potato, egg or mixtures of these. No attempt will be made to even list the numerous media and modifications which have been reported. The glycerin potato cylinder developed by Pawlowsky[96] at the Pasteur Institute has been

extensively used and the chief modification is that of Corper and Uyei[24] who used crystal violet solutions to prevent overgrowth by contaminants.

Dorset[34] used the first and simplest of the egg media. Lubenau[77] modified it by adding glycerinated extract broth, Petroff[100] by gentian violet and veal infusion, and Petragnani[99] added potato, peptone, milk and malachite green. The latter has been highly recommended by almost all who have used it. Loewenstein[76] substituted a synthetic medium containing asparagin for the peptone and added Congo red. This medium also has given excellent results. Herrold[55] added unheated egg yolk to a plain and a glycerinated agar. Jensen[59b] slightly modified Loewenstein's medium and reduced the amount of glycerin from 5 to 0.75%. This is the medium of choice among the Danish workers. Schwabacher[118] in a comparative study of many of the above media found a simple heated egg medium (3 parts yolk of egg to 1 part saline with or without glycerin) to be best suited for growing the tubercle bacilli. In 1938, Boissevain and Schultz[15] discovered that the growth factor in the egg yolk is an alcohol soluble lipoid and this is also to be found in the liver and spleen of guinea pigs and rats.

It would appear that good results can be obtained by a variety of media and in the hands of the experienced worker the simplest medium is as satisfactory as the most complicated.

Differentiation. Differentiation of bovine human tubercle bacilli depends upon: (1) The slow growth of colorless moist colonies of the bovine (dysgonic) as contrasted with the more actively growing, dry pigmented colonies of the human (eugonic) (the latter being definitely enhanced by the use of glycerin which tends to inhibit the bovine type); (2) the high degree of pathogenicity of the bovine, the low or total lack of pathogenicity of the human for the rabbit. Both, of course, are highly pathogenic for the guinea pig.

Incidence. The total incidence of bovine tubercle bacilli in human tuberculous infection is approximately 10%. This is based upon the analysis of about 18,000 strains reported from various parts of the world. The geographic distribution of these bovine infections is extremely interesting. The greatest number occurred in Great Britain (Scotland having the highest figure in all varieties of infection) (Table 1), Denmark (Table 2) coming next. These two countries, it should be noted, have done by far the greatest amount of research on this problem. Germany is next in the list, but since few recent statistics are available no conclusions are justifiable. The figures for the remaining European countries are fragmentary and are of academic rather than scientific value. The statistics for the United States are based chiefly on the reports of Park and Krumwiede,[94] Aronson and Whitney,[6] van Es,[39] and Chang.[22] The surprising results given by Chang probably do not represent present-day conditions. However, vital statistics from the United States show that a direct parallelism exists between the eradication of tuberculosis in cows and the striking reduction in mortality from extrapulmonary forms of tuberculosis.

Table 3 shows the reported incidence in various countries, excepting Britain and Denmark. In determining the number of cases of bovine infection in various countries it must be realized that the amount and the quality of the bacteriologic diagnoses vary within very wide limits. The figures presented are, therefore, at best nothing more than an

approximation of the total number of cases of bovine infection in man, but the more reliable British and Danish results are sufficient to show clearly the importance of the problem.

There are a number of interesting phases in the bacteriologic analyses of the materials which will be considered under separate headings.

Mixed and Double Infections. A mixed infection is one in which both types of tubercle bacilli are present in the same site. The discovery of such infections was made possible by the inoculation of rabbits and the observation of the types of growth in cultures. Differentiation by the characters of the colonies is the safer method since it eliminates the possible spontaneous infection of the inoculated animals. There have been reported 25 such cases. Kossel[64] reported such isolations from the sputum of a case of pulmonary tuberculosis, Lindemann[74] a similar case, Lange[66a] the same, Daddi and di Natale[30] 2 such cases, Valtis, Paisseau and van Deinse[132] 1 from the gastric washings of an infant, and Ruys[111a] 2 cases from similar material. Jensen[59c] reported 6 cases of mixed infection from Denmark, all these patients were suffering from ulcerative pulmonary tuberculosis. In 5 of the 6 cases the organisms from the sputum showed two distinct types of colony. In the sixth case, bovine tubercle bacilli only were recovered from the sputum; but at autopsy human and bovine bacilli were isolated from the lungs, liver, spleen, and mesenteric glands while a bronchial gland yielded human bacilli only.

In Great Britain 9 cases of mixed infections are reported among some 6000 cases of tuberculosis investigated bacteriologically. The cases recorded are as follows: 1, Griffith,[49a] a child dead of generalized tuberculosis. Human tubercle bacilli were isolated from mesenteric glands, lungs and meninges. Mixed human and bovine tubercle bacilli were recovered from a bronchial gland. 2, Griffith,[49a] a youth, 18 years, dead of ulcerative phthisis. A calcareous mesenteric gland yielded human and bovine tubercle bacilli. 3, Griffith,[49a] a man, aged 70 years, died of pneumonia. Human tubercle bacilli were recovered from a mesenteric gland. Mixed human and bovine bacilli were recovered from a retroperitoneal gland. 4, Griffith[49q] reported the case of a child aged 5 years who died of tuberculous meningitis. The strain from the meninges was lost. Bovine and human tubercle bacilli were recovered from a bronchial gland. 5, Cumming, Foster, Girdwood and Griffith[28] reported the case of a mixed infection in a woman of 24 years. Bovine tubercle bacilli were recovered from the sputum on several occasions, later only human bacilli. Human and bovine bacilli were recovered at autopsy from lung, bronchial and calcareous mesenteric glands. 6, In a boy of 7 years with pulmonary tuberculosis Munro[84b] reported mixed human and bovine tubercle bacilli from the sputum. 7, Munro[84b], and 8, Griffith and Munro,[51a] from 2 children under 5 years of age who died of generalized tuberculosis, obtained a mixed culture from tracheobronchial glands. 9, Griffith[49q] reported a case of mixed infection in a girl of 18 years, who died of tuberculous meningitis. A bovine strain was recovered from the meninges while mixed human and bovine bacilli were isolated from the lung. In addition, de Besche[11] reported a case from a mesenteric gland in an infant, and Goeters[44] recovered at autopsy human and bovine bacilli from the lung, and a pure culture of bovine bacilli from a mesenteric gland.

Double infections are those in which one or other type of bacillus is found in separate lesions. The number reported is 12. Kossel, Weber and Heuss[65b] reported the first case of double infection in man. They recovered at autopsy bovine tubercle bacilli from a mesenteric gland, and human bacilli from a bronchial gland. Weber and Taute[138] reported a case in a child of 5 years in which bovine bacilli were recovered from the mesenteric glands and the human type from the spleen. Park and Krumwiede[94a] in an infant obtained human bacilli from the mesenteric glands and bovine tubercle bacilli from cerebrospinal fluid. Steffenhagen[123] isolated from an infant bovine tubercle bacilli from the bronchial glands, and human bacilli from the mesenteric glands. Rothe and Bierrotte[110] obtained bovine bacilli from lupus of the nose, and human bacilli from lupus of the buttocks. Ungermann[130] reported human tubercle bacilli from the knee joint, and only on one occasion bovine bacilli from the sputum, in a man of 37. Lewis[73] from a butcher of 52 years found a bovine strain from a lupus lesion and human tubercle bacilli from the sputum. Blacklock[12] reported 2 cases of double infection. 1, A boy of 2 years with tuberculous meningitis who was born in the country, but had lived in the same house with a grandmother and aunt who suffered from pulmonary tuberculosis. From the tracheobronchial glands human tubercle bacilli were isolated. From the mesenteric glands a bovine strain was obtained. 2, From a child at autopsy human tubercle bacilli were recovered from the tracheobronchial glands and human and bovine bacilli from the mesenteric glands. Stürz[126] in a case of tuberculosis of the skin recovered human and bovine bacilli from two different areas. Saenz, Coste and Costil[113] in a man of 56 with tuberculosis of the skin and pulmonary tuberculosis, in whom the skin lesion had been present since 8 years of age, grew from the skin a bovine strain and from the sputum a human strain. Lange[66d] reported a case of lupus from which he isolated bovine tubercle bacilli from a skin lesion over the right knee joint, and human tubercle bacilli from the lesion of the right upper arm.

It is surprising, considering the frequency with which bovine tubercle bacilli are found in man, that mixed or double infections occur so rarely. In attempting an explanation for this it is suggested by Griffith[49q] that human and bovine tubercle bacilli rarely enter the body together. When they do, they may set up independent lesions at the different portals of entry, or they may colonize in the same gland or organ. The more frequent occurrence must be the entrance of one type at a time. If some immunity has developed as a result of the first infection the bacilli of the second infection are probably prevented from multiplying and eventually die out. On the other hand, if general resistance is not sufficiently enhanced by the first infection, the second will find conditions favorable and the bacilli are able to spread locally and into neighboring glands. It is noteworthy in connection with the cases of mixed infection recorded that the organisms were recovered from the mesenteric glands, bronchial glands and lung. There is no record of authentic occurrence of mixed infection in lesions distant from the portal of entry.

Atypical Strain. Griffith and his collaborators in Great Britain, Lange and Neufeld in Germany, Park and Krumwiede in the United States, maintained that the type is fixed. They regarded atypical

forms of tubercle bacilli as temporary variants of one or the other of the two fixed types.

Atypical strains differ either culturally or in pathogenicity from the standard, as laid down by the British Royal Commission[16,17] and rather generally accepted. The following atypical strains have been reported in the literature:

1. *Eugonic Bovine Strains.* These are those strains which grow more readily than the standard bovine strains at the time of isolation but which possess the characteristic high pathogenicity for the rabbit. There have been only three such strains reported, two by Griffith[49g] and one by Jensen and Frimodt-Moller.[60a]

2. *Dysgonic Human Strains.* These are like the bovine tubercle bacillus in *initial* cultures but show a low pathogenicity for the rabbit and may be restored to the normal human type of growth by repeated subculture on artificial culture media. The British workers have reported 37 such strains as follows: Eastwood, Griffith and Griffith[37] isolated a strain from a case of generalized tuberculosis; Griffith,[49b] 2 strains and later[49e] 2 strains from the sputum; Eastwood and Griffith,[36] 10 strains from bone and joint tuberculosis; Griffith,[49f] 5 from bone and joint tuberculosis;[49g], 1 from the cervical glands; [49h], 1 from the sputum; [49i], 2 from bone and joint tuberculosis; [49j], 1 from the meninges, and in 1932[49o] 1 from the meninges. Griffith and Munro[51b] reported 3 strains isolated from the sputum; Band, Alston, Griffith and Munro,[10] 1 from the kidney; Griffith and Smith,[52] 5 from the sputum; and Griffith and Menton,[50] 2 strains, 1 from the sputum and the second from a case of bone and joint tuberculosis. In addition, the other atypical human strains reported are as follows: Aronson and Whitney,[6] 5 strains recovered at autopsy; Daddi,[29] 39 from the sputum; Daddi and di Natale,[30] 5 more such strains. Jensen and Frimodt-Moller[60a] reported 3 such strains which they suggest might belong to the "intermediate" type (*q.v.*), and Cellina[21] 2 isolated from the kidney at operation. The work of Daddi[29] and of Daddi and di Natale[30] differs from all others in recovering such a high incidence of atypical strains, in that the 44 strains discovered were from only 542 strains isolated. The 37 strains reported by Griffith and his associates are from a total of about 6000 strains studied. The criteria used by the Italian workers would appear to be different from those of others.

3. *Attenuated Human Strains.* These are culturally typical but the pathogenicity is greatly reduced for the guinea pig. Only 3 have been reported if we except those recovered from skin lesions. These latter will be discussed later. Griffith recovered an attenuated human strain of tubercle bacilli from the cervical glands in 1917,[49g] another attenuated human strain in 1932[49c] and Jensen and Frimodt-Moller[60c] reported 1 such strain.

4. *Attenuated Bovine Strains.* These are those in which pathogenicity is reduced for the rabbit and the guinea pig, but the cultural characters are typically dysgonic. There are 26 reported, not counting those isolated from skin lesions (*q.v.*). Duval[35] recovered a strain from the cervical glands; Weber and Steffenhagen,[137] 1 from a case of bone and joint tuberculosis; Griffith,[49h] 1 at autopsy, from the bronchial glands of an infant; Munro and Cumming,[85] 2 from bone and joint tuberculosis;

Rabinowitsch-Kempner,[105b] 1 from the sputum in pulmonary tuberculosis; Griffith,[49i] 2 from bone and joint tuberculosis, and in 1932,[49p] 3 strains from various sources. Price[103b] isolated a strain from a case of multiple periarticular abscess; Daddi and di Natale,[30] 4 from the sputum, which were suggested as possible "intermediate." Cumming, Foster, Girdwood and Griffith[28] reported a strain isolated from the sputum; Griffith and Munro,[51c] 2 from the sputum; Cellina,[21] 1 from the kidney at operation; Griffith and Menton,[50] 2 from bone and joint tuberculosis; and Jensen and Frimodt-Moller[60d] reported 4 strains isolated from a gland, synovial fluid and pus from cold abscesses.

"*Intermediate*" *Strains.* As already pointed out, most workers believe that the type is fixed and that the atypical forms encountered, whether of human or bovine type, are temporary or quasi permanent variants of one or the other fixed types. The so-called "intermediate" strains reported are usually regarded as mixed strains, or as having been derived from spontaneous infection in the experimental animal (Griffith[49n]).

On the other hand, another group of workers, notable among whom are Calmette, Much, Rabinowitsch-Kempner, Jensen and Frimodt-Moller, believed that there exist transition or intermediate forms between the human and bovine types. The outstanding characteristic of these intermediate types, as pointed out by Jensen and Frimodt-Moller,[60f] is their lack of stability, both culturally and in the inoculated animal. The early conceptions of Calmette and Much have become obsolete since they were purely theoretical and no experimental work sustained them. There are reported in the literature 48 "intermediate" strains as follows: Rabinowitsch[104a] reported 6 strains recovered at autopsy (2 in primary intestinal tuberculosis, 1 in generalized tuberculosis of alimentary origin and 3 in miliary tuberculosis). Mohler and Washburn[81] had 1 strain from sputum. Dammann and Rabinowitsch[32] reported 1 strain isolated from the skin which culturally was of human type but which possessed an attenuated bovine type of pathogenicity for the rabbit. Duval[35] reported 1 strain from the cervical glands; Lindemann,[74] 1 from the sputum; Rabinowitsch-Kempner,[105a] 3 from lupus lesions; Aronson and Whitney,[6] 2 from the lung at autopsy; and Mozer and Mozer,[82] 3 from bone and joint tuberculosis. These latter writers did not indicate the cultural characters of these strains, but stated that biologically they were of "intermediate" virulence for rabbits, suggesting to the Reviewer that they were probably attenuated bovine strains.

d'Asaro[7] reported an intermediate strain recovered from a case of multiple bone and joint tuberculosis and suggested a mutation of type, but to the Reviewer his results are most simply explained as due to technical error. Valtis and van Deinse,[131] and Bablet, Valtis and van Deinse[8] reported 21 strains which they identified as "intermediate" and which they had recovered through guinea pig inoculation, some of the animals subsequent to inoculation having been treated with an acetone extract of the Koch bacillus. (See Negre technique above.) Culturally, these strains suggested an atypical bovine type of the tubercle bacillus, but rabbits inoculated with 1 mg. and 0.1 mg. failed to develop the lesions which would have facilitated the identification of type. They classed these strains tentatively as "intermediate." Bablet and

Bloch[9] had a strain from the skin. Jensen and Frimodt-Moller[60] reported 7 strains of tubercle bacilli isolated from the urine, sputum, pleural fluid, gastric washings, sputum and 2 from lupus. In a comprehensive study the authors pointed out the following characteristics of these 7 strains: (*a*) Four grew less eugonic, but distinctly differed from the bovine type; (*b*) all 7 strains were of low virulence for the rabbit, like the human type, but in all 7 the authors were able in at least 1 rabbit, and in one instance in 3 inoculated rabbits, to demonstrate bovine tubercle bacilli. They used careful controls against spontaneous and mixed infection, and concluded that the appearance of typical bovine tubercle bacilli in the passage animals were due to the transformation of the original strains.

The term "intermediate" involves the conception of mutation of type. This may appear an attractive theory on purely theoretical grounds, but there has not been enough satisfying evidence to support such a conception. Were it not for Rabinowitsch-Kempner and Jensen and Frimodt-Moller, who are among the most authoritative workers in the field of tuberculosis, one could dismiss these views as being fallacious on various technical grounds. Griffith,[49n] on the basis of vast experience, has failed to bring about transmutation of type under any experimental conditions nor could he obtain any convincing evidence for its occurrence in the natural infection in man. Animal passage using various types of animals and over different periods of time up to 3 years did not bring about any change suggesting transmutation. He took particular care in these experiments against spontaneous infection in his animals which if it had occurred would naturally have confused the issue. There was no certain evidence that the bovine tubercle bacilli change into human bacilli during residence in the human body, but there is ample evidence that they may retain their cultural and biologic qualities after prolonged sojourn in man. Notable in this regard are the typical bovine tubercle bacilli isolated by Griffith[49r] from tuberculosis of the skin, 13 to 52 years after infection (average 22 years) and from many cases of bovine phthisis in the adult dating back to early childhood.

Tuberculosis of the Skin. A striking feature regarding the tubercle bacilli isolated from the skin is that about one-half of the strains of human type and about two-thirds of the bovine strains show a marked degree of attenuation of pathogenicity for both the guinea pig and the rabbit. Calmette[20] gave the feature of attenuation of the tubercle bacillus from skin lesions as the reason "why no one has ever been successful in inoculating lupus from one human being to another," although no mention is made of any experiments for this purpose.

There are reported 718 strains of tubercle bacilli isolated from various forms of tuberculosis of the skin. Of this number 503 were of human and 215 (29.9%) of bovine type. A detailed analysis of 375 strains showed that 229 were of human, 134 of bovine type and 12 were listed as "intermediate." Of the 229 human strains, 117 (51%) were typical culturally and biologically, and 112 (49%) were definitely attenuated. Of the 134 bovine strains isolated, 49 (36.6%) were typical culturally and of standard virulence for experimental animals, and 85 (63.4%) were attenuated.

The following are the published reports: Burnet[19] isolated 10 strains of the human type from lupus—of these 9 were of standard virulence and 1 was attenuated; Gossio,[47] 15 human type strains, all of attenuated virulence; Andersen,[4] 28 strains, 18 were human tubercle bacilli of which 9 were of standard and 9 of attenuated virulence, and 7 bovine strains of which 4 were of standard and 3 of attenuated virulence. In addition, he had 3 "intermediate" strains. Kirchner[61] reported 23 strains, 11 of human type and 12 of bovine. Of the human strains, 9 were of standard and 2 of attenuated virulence. Of the 12 bovine strains, 5 were of standard and 7 were attenuated in virulence. Rabinowitsch-Kempner[105a] had 18 strains; of these, 12 were of standard human type, 3 of standard bovine type and 3 strains she classified as "intermediate." Holland[57] isolated 32 strains of tubercle bacilli, 30 of human and 2 of bovine type. In the 30 human strains 22 were of standard virulence and 8 were attenuated. Of the 2 bovine strains, 1 was of standard and the other of attenuated virulence. Bronstein and Liudvinovski[18] isolated 17 strains, and of these 13 were of standard human virulence, 2 were of standard bovine type and 2 they classified as "intermediate."

Griffith,[49p] in a comprehensive study of 188 cases of tuberculosis of the skin investigated by him during the years 1907–1932, found that 95 of the cases were due to the human type of the tubercle bacillus, and 93 to the bovine type. Of the 95 human strains, 34 (35.7%) were culturally and biologically typical, and 61 (64.2%) were attenuated. Of the 93 bovine strains, 31 (33.3%) were culturally and biologically of standard bovine type and 62 (66.6%) were attenuated. Sato[115] reported 9 isolations from tuberculosis of the skin, 6 were of human type and 3 of bovine. All the human strains were typical. Of the 3 bovine strains, 1 was of standard bovine virulence and 2 were attenuated. Jensen and Frimodt-Moller,[60d] in 35 cases of skin tuberculosis, found in 19 the human type of bacillus, in 12 the bovine and in 4 an "intermediate" type. Of the 19 human strains, 3 were of standard virulence and 16 attenuated; of the 12 bovine strains, 2 were of standard virulence and 10 attenuated. Fourteen cases of lupus reported from America gave the following results: Ravenel[107] (who was probably the first to isolate a bovine bacillus from man) obtained a bovine strain; Hess[56] reported 2 bovine strains; Park and Krumwiede, in 1911,[94b] 1 human strain; and Lewis,[73] 1 bovine strain. Price[103e] isolated 9 strains, 8 human and 1 bovine. There is no indication that any of these American strains were of other than standard type.

Bovine Phthisis. This term designates pulmonary tuberculosis in man caused by the bovine type of the tubercle bacillus. The most important information recently brought to light is the fact that the bovine type of the tubercle bacillus can and does produce tuberculosis in the human lung. The investigation of this question followed the dogmatic statement of Robert Koch, in 1908, that pulmonary tuberculosis in man was not caused by the bovine bacillus. Up to 1914, outside of the British Isles, there were reported 926 strains of tubercle bacilli isolated from the sputum. All of these were of the human type and in only 3 instances bovine strains were also present.

In the British Isles, Griffith reported, in 1909, 2 cases of bovine tuberculosis of the lung from England[49a] and, in 1913, 1 case from

Edinburgh,[49b] and in 1916 Wang[135] reported another case from Edinburgh in a man of 41. No new cases were reported from Britain until 1922, when Munro discovered 2 cases of bovine phthisis near Edinburgh (Munro and Griffith[86]). An intensive investigation followed Munro's finding. In Scotland, and later in the north of England, cases came to light relatively quickly and it became evident that bovine phthisis in man occurred much more frequently than had been previously thought possible.

Up to September, 1937, there were reported a total of 320 cases of bovine phthisis. Of this number, 163 have been reported from Great Britain (Table 1).

TABLE 1.—INCIDENCE OF BOVINE TUBERCULOSIS IN MAN IN GREAT BRITAIN. (GRIFFITH.[49f])

	English statistics.				Scottish statistics.			
		Percentage of cases infected with bovine type of bacillus.				Percentage of cases infected with bovine type of bacillus.		
Variety of tuberculosis.	No. of cases.	Under 5 yrs.	5 to 15 yrs.	All ages.	No. of cases.	Under 5 yrs.	5 to 15 yrs.	All ages.
Cervical gland	126	90.9	53.4	50.0	93	65.0	62.3	51.6
Lupus (skin)	191	58.4	44.4	48.7	13	100.0	71.4	69.2
Scrofulodermia	60	53.3	43.3	36.6				
Bone and joint	553	29.5	19.1	19.5	218	46.2	28.9	29.8
Genito-urinary	23	..	..	17.4	42	..	..	31.0
Meningeal	265	28.1	24.5	24.6	203	34.4	14.0	29.6
Autopsies	187	28.6	15.5	22.5	290	33.6	38.5	32.4
Miscellaneous	23	33.3	9.1	8.7	14	..	..	71.4
	Total.	Human.	Bovine.	Bovine. %	Total.	Human.	Bovine.	Bovine. %
Pulmonary	3254	3198	56	1.7	2051	1944	107	5.2

TABLE 2.—INCIDENCE OF BOVINE TUBERCULOSIS IN MAN IN DENMARK. (JENSEN AND FRIMODT-MOLLER.[60b,c])

	Up to 15 yrs.			15 to 30 yrs.			30 yrs. and over.		
	Total.	Bovine.	%.	Total.	Bovine.	%.	Total.	Bovine.	%.
Respiratory	1824	88	4.8	432	29	6.7	1007	50	5.0	385	9	2.3
Bones and joints	567	105	18.5	98	24	24.5	255	57	22.4	214	24	11.2
Glands	251	123	49.0	80	66	82.5	97	47	48.5	74	10	13.5
Meninges	304	75	24.7	176	58	33.0	92	13	14.1	36	4	11.1
	2946	391	13.3	786	177	22.5	1451	167	11.5	709	47	6.6

In Scotland, Griffith and Smith,[52] Griffith and Munro,[51] Griffith,[49b] and Wang[135] reported in all 2051 cases of pulmonary tuberculosis of which bovine tubercle bacilli were found in 107 instances (5.2%). In England, Cumming,[27] Edwards, Lynn and Cutbill,[38] Griffith and Menton,[50] Griffith,[49r] and Cumming[27c] reported bovine tubercle bacilli in 56 (1.7%) of 3254 cases of pulmonary tuberculosis. In Wales, Cumming found 2 cases (1%) of bovine phthisis in an analysis of 203 cases (included in the English figures) of pulmonary tuberculosis (Griffith[49r]) The geographic distribution of bovine phthisis in Britain is very interesting. It increases in frequency from the south to the north of England. The highest incidence occurred in northeast Scotland, and has a direct relationship with the incidence of tuberculous infection in cattle as indicated by Griffith.[49r] In striking contrast with the English,

Welsh and Scottish findings are the findings of Cumming[27c] for the Irish Free State. In an examination of 320 cases of pulmonary tuberculosis, not a single bovine strain of the tubercle bacillus was recovered. It is perhaps significant in this regard that Coffey[23] considered that bovine tuberculosis in the Irish Free State was definitely under control.

In Denmark, Jensen and Frimodt-Moller[60b] recovered 88 strains of bovine tubercle bacilli from among 1824 cases of pulmonary tuberculosis (4.8%). The distribution of bovine phthisis in Denmark is very instructive: only 1.6% occurred in Copenhagen and the islands; 5.4% in north and east Jutland, and 13% in west and south Jutland, the distribution corresponding directly with the prevalence of tuberculosis in cattle. In Holland, in 468 cases of pulmonary tuberculosis studied, 29 (6.2%) proved of bovine origin. Ruys[111a] found bovine tubercle bacilli in 3 out of 115 cases in Amsterdam, and in 10 out of 89 adults in north Holland, giving a percentage of 6.4 for her 204 cases.

TABLE 3.—THE INCIDENCE OF BOVINE TUBERCULOSIS IN MAN.

Country.	Total number.	Human.	Bovine.	Bovine, %.
France[5,9,26,33,68,108,109,112b,132]	1083	1055	28	2.6
Germany[67]	1165	1007	158	13.5
Netherlands[14,72,111,133]	767	701	66	8.6
Switzerland[106,117,124]	218	201	17	7.8
Sweden[64]	14	14	0	0
Norway[3,11,57,123]	107	101	6	5.6
Poland[101]	160	149	11	6.9
Italy* [7,21,29,30,47,98,116]	871	846	25	2.9
Spain[25]	95	90	5	5.3
Hungary[58,128]	334	328	6	1.8
Greece[2]	327	327	0	0
Australia[97,139]	280	246	34	12.1
Japan[1,62,63,78,115,141]	272	264	8	2.9
United States[6,22,39,40,45,46,56,73,75,79,92,93,94,107,120,121]	1362	1202	160	11.7
Canada[103]	901	847	54	6.0

* In Italy there were 64 atypical strains.

In Germany, in an analysis of 495 cases of pulmonary tuberculosis, 16 (3.2%) proved of bovine type. Most noteworthy is the work of Lange[66c] who reported 12 cases in this series. He particularly emphasized the fact that 8 of the 12 cases of bovine tuberculosis of the lung occurred in individuals whose occupation brought them in close contact with cattle, such as milkers, stablemen and so on. In Italy, Daddi,[29] Daddi and di Natale,[30] and Savagnone,[116] and Pergola[98] reported that in 639 cases studied they found 16 (2.4%) of bovine type. In Hungary, Szüle (1936)[128] reported 2 cases of bovine phthisis in 206 cases studied (0.9%). In Switzerland, Strempel and Mündel[124] reported 1 case in 60 studied. In France, from a total of 561 cases, Saenz[112a] and d'Arcier and Mme. d'Arcier-Borrel[5] reported 2 of bovine type (0.4%). In Poland, Piasecka-Zeyland,[101] of 112 cases studied, reported 3 (2.7%) of bovine type.

Of great importance is the work done by Griffith[49r] and his collaborators in the survey of bovine phthisis in Great Britain. In 67 of the cases reported he isolated the organism himself and 95 strains were submitted to him for further study by Munro, Cumming and Lynn.

In 13 cases the results of the sputum examination were also confirmed by isolating in each case identical strains at autopsy. Two cases yielded mixed human and bovine bacilli; 5 strains isolated in this series showed attenuation in virulence—the remaining 8 strains were culturally and biologically typical bovine. The extent of tuberculous involvement in these cases of bovine phthisis varied from a limited lesion in one lobe to widespread bilateral disease; and in character from acute exudative tuberculosis to chronic fibrosing disease, lasting many years and in some instances becoming quiescent and sputum negative. Bovine phthisis is clinically and radiographically indistinguishable from infection due to the human bacillus. Of the 13 cases that came to autopsy, 8 showed evidence of disease in the mesenteric glands—obviously older than the lesion in the lung. The anatomic evidence strongly favored the alimentary tract as the portal of entry in these cases. In 5 of the remaining 13 the portal of entry was not conclusive. Griffith reported 4 further cases of alimentary tuberculosis with pulmonary cavitation in the lung due to bovine bacilli. The bacilli were recovered from the organs after death but had not been obtained from the sputum during life. Three occurred in children under 5 years, and 1 in an adult of 21, with bilateral cavitation in the apex of each upper lobe. Thus, in the opinion of Griffith[49] and his collaborators, the portal of entry of the tubercle bacillus in bovine phthisis is by the alimentary tract—usually as a childhood infection and the dissemination occurs by the blood stream, in contrast to human phthisis where the portal of entry is by the respiratory tract.

Lange,[66] on the other hand, believed that the infection of the lung with the bovine tubercle bacillus is often an inhalation infection through contact with tuberculous cattle, and occurs in adult life. Tobiesen, Jensen and Lassen[129] agree with the British workers regarding the portal of entry by the alimentary tract, but they cannot overlook contact infection as a possibility. In this regard they pointed out that Blegvad and Jensen (1935) isolated bovine tubercle bacilli from 6 cases of primary tuberculous conjunctivitis in milkers.

There is *no* convincing evidence of human-to-human transmission of bovine tubercle bacilli (Walker),[134] but there is clinical and anatomic evidence of alimentary infection. In fact, Griffith[49r] stated that in Britain, at least, bovine phthisis is caused by infection acquired in childhood, adolescence or even adult life, through the consumption of infected cow's milk.

Milk in Its Relation to Tuberculosis in Man. The incidence of bovine tuberculosis in man depends upon the amount of tuberculous infection in cattle with its subsequent milk infection, and is directly influenced by the custom prevailing in the community of feeding infants and children raw milk. Milk can be contaminated from the cow in a number of ways: 1, Indirectly by contamination of the milk, while milking, with droplets or dust from the sputum, or from the dust of dried feces of the infected cow; 2, directly by the bacilli from lesions in the cow's udder. This is the less common but much more dangerous form of contamination. Table 4 is merely a collection of condensed statistics on the findings of tubercle bacilli in raw milk. Most of these results no longer represent the present-day condition, many are too few to be of any statistical value, but in a broad way the table suggests

the extent of the danger of infected milk. The circumstantial evidence is so strong that few question that milk is the source of the infections in human cases; direct proof in specific cases is rare, but has been accomplished by Park and Krumwiede,[94] and Price.[103d] There have been at least 2 human experiments using bovine tubercle bacilli. Weber,[136] in an experiment to confirm Koch's contention that the bovine tubercle bacillus was of low pathogenicity for man, fed 360 individuals, of whom 151 were children, with raw milk from tuberculous cows. Only 2 cases of cervical adenitis developed in this group. Szampan,[127] in Zürich, reported the development of a cold abscess at the site of an intramuscular inoculation of milk in 2 infants.

TABLE 4.—BOVINE TUBERCLE BACILLI IN RAW MILK. (GERVOIS.[43])

	Number.	Bovine.	%.
South of England	12,324	917	7.4
North of England	39,620	3228	8.1
Scotland	21,461	979	4.5
United States	1,476	126	8.5
Canada	200	8	4.0
Argentine Republic	17	3	17.6
India (Bombay)	600	0	0.0
Australia	1,016	1	0.09
Germany	3,395	289	8.5
Denmark	28	4	14.2
Spain (1936)	200	16	8.0
France	58	6	10.3
Greece	35	0	0.0
Italy	544	37	6.8
Netherlands	200	4	2.0
Poland	297	67	22.5
Russia	73	3	4.1
Switzerland	245	20	8.1
	81,789	5708	6.97

The evidence for milk as a source of the bovine infection in man has been accumulated by workers all over the world. Fraser[42] pointed out that among the children with bovine infection a large number had been fed raw milk. Mitchell[80] found in a group of 19 patients fed raw milk, bovine tubercle bacilli from the cervical glands in 17. Griffith, in England,[49r] Griffith and Summers,[53] and Munro and Walker,[88] in Scotland, Park and Krumwiede[94] and Chang,[22] in the United States, Price,[103c] in Canada, and Boer,[14] in the Netherlands, have drawn attention to contaminated milk as the source of tuberculous infection in children. In Poland, Piasecka-Zeyland and Sznajder[102] mentioned a case of bovine tuberculosis in a patient of 24 years who until the age of 15 years had had raw milk. Tobiesen, Jensen and Lassen,[129] in Denmark, emphasized that 13 of the 26 cases of bovine phthisis they investigated gave a similar history. Strempel and Mündel,[124] in Switzerland, pointed out their cases of bovine infection had been fed raw milk. In Aberdeen, Griffith and Smith[52] found that 12 out of the 13 patients with bovine phthisis were in the habit of drinking raw milk. Ruys[111a] noted the same conditions in 23 of 33 cases of bovine tuberculosis in Amsterdam. In France, Lesné, Saenz, Salembiez and Costil[70] found that 8 of the 9 cases of tuberculous meningitis in children caused by the bovine tubercle bacillus had been fed raw milk, and they all

lived in rural districts. Munro and Scott[87] found that the children under 2 years who died of tuberculous meningitis had been fed raw milk. They stressed in their cases the lack of contact with known human tuberculosis and concluded that milk was the source of the infection.

Griffith[49r] stated for England that "5 to 12 per cent, and more, of samples of ordinary milk contain tubercle bacilli, and more than one third of the milking cows in this country are tuberculous," while in northeast Scotland he reported, in 1936, that 40 to 90% of the cows in 6 milking herds reacted to tuberculin and in one small district no less and 15 of 53 cows in one herd showed udder tuberculosis. Dalrymple-Champneys[31] stated that no less than 80% of the samples of milk brought to London in tanks for pasteurization were infected with tubercle bacilli. In Denmark, as already mentioned, this same relationship has been shown to exist between bovine infection in man and the disease in cattle.

Control of Bovine Tuberculosis in Man. The part taken by bovine strains of tubercle bacilli in the problem of human tuberculosis is no longer questioned. Bovine tuberculosis in man can be completely eliminated in one of two ways: 1, the eradication of the disease in its natural host by tuberculin testing and the slaughter of reactors; 2, by the universal pasteurization of all milk used for human consumption.

The application of the first of these methods in the United States had resulted (Wight)[140] in the very striking reduction from an incidence of 10% infection in cattle in 1908 to 0.7% in 1936. In 1918, there were 4.9% reactors; in 1924, 3.2; in 1928, 2.3; in 1929, 1.8; in 1930, 1.7; in in 1934, 1.6; in 1935, 1.5; and in 1936, only 0.7%. The result in 1936 involved the testing of 23 million cattle. In this same year among 10 million cattle (not including reactors) slaughtered for food evidence of tuberculosis was found in only 0.19%. It would seem that this marked reduction in bovine tuberculosis has been reflected in the striking drop in the death rate from extrapulmonary forms of tuberculosis in man from 22 per 100,000 in 1916 to 5 per 100,000 in 1937 (Smith).[119] The figure shown in Table 3 indicating an incidence of 11.7% for bovine tuberculosis in man in the United States has been influenced by the recent results reported by Chang[22] from Lakeville State Sanatorium (Massachusetts). The Reviewer cannot believe that his figure represents the situation in the United States today in that of his 200 cases, 55 (27.5%) were of bovine type. The results of Park and Krumwiede[94] and Park[93] show from 564 cases an incidence of 7.6% bovine infection, while the results of Aronson and Whitney[6] and van Es[39] give 3.8 and 3.9%. It is highly desirable in view of the splendid results obtained in the eradication of tuberculosis in cattle that a great many more statistics should be obtained for the United States showing the incidence of bovine infection in man both in pulmonary and extrapulmonary infections.

As an example of the efficacy of supervised pasteurization of milk the city of Toronto offers the best example available in the literature. Since 1916, when pasteurization was made compulsary, there has not been a single proven case of bovine infection in the generation of children using the city milk. Price[103d] bases this contention on a bacteriologic study of nearly 500 tuberculous children.

In reviewing the incidence of bovine infection in man in the various countries it is to be noted that the correlation is often very poor between bovine infection in cattle and the incidence of the bovine type of infection in man. France, Greece and Poland are striking examples showing this lack of correlation. The explanation for this we believe is to be found in the household custom of boiling milk, as an economic procedure to prevent it from going sour. Thus unconsciously the children of these countries have escaped bovine tuberculosis which is so common in other European countries.

Summary. The bovine tubercle bacillus has been shown to be a factor of considerable importance in human tuberculosis, particularly in children, accounting for approximately 10% of such cases. The distribution, character of the lesions and the outcome of the infection are the same in both types of infection. The most important difference, however, is that the bovine infection can be eliminated by practical methods which have been shown to be highly efficient.

The most important recent advances in our knowledge have been in the studies of bovine phthisis and it has been shown that the relationship between it and the tuberculous infection in cattle in this form of bovine infection in man is essentially the same as in the extrapulmonary forms of the disease.

R. M. Price, M.B.

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HYGIENE AND PUBLIC HEALTH.

UNDER THE CHARGE OF

KENNETH F. MAXCY, M.D.,

PROFESSOR OF EPIDEMIOLOGY, SCHOOL OF HYGIENE AND PUBLIC HEALTH, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD.

THE STATUS OF PERTUSSIS VACCINE IN THE PREVENTION OF WHOOPING COUGH.

In 1931, the Council on Pharmacy and Chemistry of the American Medical Association voted to omit pertussis bacillus vaccines from the list of new and non-official remedies in view of the fact that in 15 years

of extensive use no acceptable confirmatory evidence for their value had become available. In the past 8 years the whole subject of the use of pertussis vaccines in the prevention of whooping cough has been reviewed. Some of the reasons for previous failures have become apparent. Definite progress has been made and recent studies indicate that it is possible by artificial immunization to increase definitely the resistance against infection and to prevent, or to reduce the severity of, clinical attack.

Etiologic Relationship of H. pertussis. The rationale of the preventive use of pertussis vaccine depends fundamentally upon the primary etiologic relationship of this organism to the disease whooping cough. In 1932, Rich reviewed the evidence and found it unconvincing. He called attention to a number of considerations which were consistent with the hypothesis that the disease was primarily due to a virus which paved the way for secondary invasion by *H. pertussis*, *H. influenzæ*, and possibly other organisms. Without reviewing these considerations in detail, it suffices to state that subsequent work has failed to establish the existence of the hypothetical virus, and, on the other hand, observations on experimental animals and human beings have confirmed the case for *H. pertussis* as the primary incitant (Farber and Wolbach,[8] 1932; Sprunt, Martin and Williams,[27] 1935; Rich *et al.*,[21] 1932; MacDonald and MacDonald,[17] 1933; Miller,[18] 1933; and Gallavan and Goodpasture,[9] 1937). While it is undoubtedly true that pertussis-like coughs may occasionally be caused by atypical organisms such as *B. parapertussis* (Eldering and Kendrick,[7] 1938; and Bradford and Slavin,[2] 1937), *A. bronchisepticus* (Brown,[3] 1926), and possibly also *H. influenzæ* (Rich,[20] 1932), such studies as those of Gardner and Leslie[10] (1932), Kristensen[13] (1933), Sauer[22] (1933), and Kendrick and Eldering[12a] (1935) have shown beyond all question that *H. pertussis* is the organism commonly associated with this condition.

Methods of Producing Pertussis Vaccine. The primary etiologic relationship of *H. pertussis* having been established, successful immunization waits upon the development of an effective antigen. Although Sauer and others had empirically used freshly isolated strains, the fundamental necessity of this requirement was emphasized by the work of Leslie and Gardner[16] (1931). They pointed out that although *H. pertussis* is a uniform species without fixed varieties or types, when it is subcultured on artificial media it tends to go through a series of regressive changes corresponding to the smooth→rough variation which has been found to occur with many other species of bacteria. They described 4 phases in this change, Phases 1 and 2 being identified with the smooth, and 3 and 4 with the rough colony variation. Their observations have been confirmed in all important essentials by Shibley and Hoelscher[24] (1934), Toomey, Ranta and Takacs[28] (1935), Lawson[15] (1939) and others. It has been established that with the variation toward the rough colony type the organism tends to lose its capsule, is altered antigenically, becomes less toxic for guinea pigs, rabbits and mice, and is no longer infective for the chimpanzee (Shibley.[23] 1934).

This variation afforded an explanation for the failure of the vaccines formerly produced. It became clear that the primary requisite for an effective pertussis vaccine was the use of freshly isolated and Phase 1 strains.

Because of previous failures, Sauer also advanced the idea that it was necessary to increase the dosage from 3 injections, with a total of 22,000,000 bacteria or less, to a dosage of 70,000,000 to 80,000,000 bacilli or more, given in 3 or 4 bilateral injections at intervals of 1 week. It was pointed out that full protection could not be expected until 2 to 3 months after the vaccine was injected. The discussion in this paper is confined to vaccines made and administered according to these general principles to prevent or modify clinical attack.

Laboratory Appraisal of Immunizing Value of Vaccines. No laboratory method has yet been devised which is satisfactory for assay of the immunizing value of a pertussis vaccine. The production of agglutinins, opsonins, precipitins, and complement fixing antibodies in animals is obviously inadequate. Burnet and Timmins,[4] Bradford,[1] Powell and Jamieson,[19] Silverthorne,[25] Lawson[15] and others have explored the possible use of white mice. It has been shown that they can be actively immunized by injection of a suitable antigen. The test for the presence of immunity carried out later—production of pneumonia after intratracheal injection or production of death after intraperitoneal injection—is so crude and variable that it is as yet far from satisfactory.

It has long been known (Gundel, Keller and Schlüter,[11] 1935; and Kristensen and Larsen,[14] 1926) that complement fixing antibodies and/or agglutinins can be demonstrated in a very large proportion of patients with whooping cough 3 or 4 weeks after onset. Daugherty-Denmark[5] (1936) has found these antibodies present in the serum of patients a month or more after the third injection of Phase 1 pertussis vaccine. It has not yet been proved, however, that their appearance is a necessary accompaniment of active resistance to the disease, nor that their absence is an indication of susceptibility.

Clinical Appraisal of the Immunizing Value of Vaccines. Lacking satisfactory laboratory test, the immunizing value of a pertussis vaccine *can only be determined by human trial.* The conditions of this trial must be such as to permit unbiased judgment. This implies that along with a large group of injected children an equivalent group of non-injected controls must be kept under observation, that the opportunity to detect and definitely diagnose clinical attacks of whooping cough must be equal in the two groups; that the period at risk must be the same; and that the length of time must be sufficient to afford opportunity for a significant and equally distributed number of natural exposures to occur. As all who have had experience know, this is an ideal which can be approached but never completely realized in dealing with human beings under natural conditions. Nevertheless, there have become available during the past 7 years a number of reports of studies of the immunizing value of Phase 1 pertussis vaccine which present evidence worthy of note.

Sauer began his observations in 1928 and has published a series of reports, modifying his procedure from time to time. In 1937 he gave a summary of the experience of Evanston's municipal whooping cough clinic. During a 3-year period, 1122 children with an average age of 10 months had completed pertussis vaccinations. The nurses of various agencies in close daily contact with contagious disease situations reported to the Department of Health (*i. e.*, discovered) that 128 of these children had subsequently been exposed—94 within the house-

hold and 34 outside the family—to other children who had whooping cough. Six injected children (4.7% of those so exposed) developed the disease. The clinical course in 5 was mild, in 1 it was quite severe. Sauer did not present for comparison an equivalent group of non-injected children in this publication. Recourse must be taken to general experience. It is conceded that ordinarily 70% or more of young children who have not been immunized may be expected to contract whooping cough when exposed to another case within the household. Sauer's most recent experience (1939) is summarized in the following tabulation:

CONTROLLED VACCINATIONS WITH AUTHORIZED HEMOPHILUS PERTUSSIS VACCINE* (JANUARY 1, 1933, TO OCTOBER 1, 1938), AGE RANGE 6 MONTHS TO 4 YEARS.

Groups.		No.	Contracted whooping cough. No.	%
Private, from 1933 . .	Unvaccinated (controls)	560	105	18.8
	Vaccinated	1001	16	1.6
Evanston Dept. of Health from 1934	Unvaccinated (controls)	1100	129	10.8
	Vaccinated	1377	10	0.7
St. Vincent's (1935 epidemic)	Unvaccinated (controls)	70	52	74.2
	Vaccinated	75	6	0.8
Totals	Unvaccinated (controls)	1730	286	16.5
	Vaccinated	2453	32	1.3

* Since March 1, 1938, only "double strength" vaccine (1 cc. = 20,000 organisms) has been used; total dosage from 80,000 to 100,000 million.

The article does not contain a definite statement as to the comparability of test and control groups. It is not clear just how long these children have been kept under observation, to what extent they have suffered exposure, and how effective the machinery was for detecting the clinical attacks which occurred in both groups. If comparability be conceded then the frequency of attack among the unvaccinated was about 12 to 13 times that of the vaccinated group. The net observation of 2453 vaccinated children over periods varying from a few months to 5 years, with only 32 clinical attacks of whooping cough having been reported among them in a city the size of Evanston, would seem in itself to imply that a considerable degree of resistance must have been conferred.

Since 1932 a comprehensive program of study of the immunizing value of pertussis vaccine has been under way in Grand Rapids, Mich. A progress report was made by Kendrick and Eldering,[12b] in 1936, and the final analysis[12c] was presented at the 1938 meeting of the American Public Health Association. The total time period covered by the observation is 44 months. There was gradually accumulated an inoculated and a control group of children of the age range 8 months to 6 years. They were admitted and discharged from the study after varying periods of time, and while in the study kept under observation and checked by repeated nursing visits. Final analysis was based upon 1815 children, representing 2268 person-years of experience, in the injected group, and 2397 children, representing 2307 person-years of experience, in the control group. While the average period of observa-

tion for the whole group was 13 months, 25% of the children were under observation less than 6.5 months and 75% less than 17.7 months. Detailed statistical comparisons indicated that the test and control groups were similar in respect to conditions affecting susceptibility and exposure to pertussis infection. The attack rate (expressed upon the basis of 100 persons at risk for 12 months) was 2.3 in the injected and 15.1, or more than 6 times as great, in the control group. The difference is about 15 times the standard error. By various other methods of comparison, the advantage was found to be consistently in favor of the injected group. For example, among 83 of the injected group who were exposed to infection within the household, 29 (34.9%) developed clinical attacks, while among 160 of the control group similarly exposed, there were 143 (89%) attacked. The data are convincing that vaccine as made and administered in this study afforded a considerable degree of immunity against clinical attack for a period of approximately 1 year.

In 1934, Doull, Shibley and McClelland[6] set up a study of active immunization against whooping cough in Cleveland. An interim report was made in 1936; final report is in press. Between June, 1934, and July, 1935, 483 Cleveland children between 6 and 15 months of age were given whooping cough vaccine. All save 61 received full dosage. A total of 496 children of comparable ages and living in the same neighborhoods were selected as controls. Children of both groups were kept under careful observation from June 24, 1934, to September 12, 1936. There had occurred 61 attacks among inoculated and 71 among control children. Thus the attack rate during this period was not significantly lower among the inoculated, although there was some evidence that their attacks were milder than in the non-inoculated.

The evidence was collected so carefully in this study that one cannot escape the conclusion that the injection of pertussis vaccine—as prepared by these authors—had very little, if any, effect in preventing clinical attack, although it may have reduced severity.

At Stanford University School of Medicine Children's Clinic, a study in pertussis immunization has been going on since 1935. A preliminary report was given by Miller in 1938. Up to the time of the report 206 children had been enrolled in the injected group and 181 in the control group. The great majority in both were babies between 6 and 10 months of age at the time of entrance into the study. They were apparently followed through clinic visits. In the test group there have been 26 known exposures and 8 cases; in the control group, 19 known exposures and 29 cases. The crude attack rate % in the former is 3.9% as compared with 16% for the latter. Presumably the information is equally complete (or deficient) with regard to both groups.

Since 1935 a similar study has been in progress in the out-patient department of the University of California, upon which Singer-Brooks[26] has made a preliminary report. Immunizing injections were given to children more than 5 months of age. Sibling controls were used rather than alternate patients. Definite appointments for follow-up visits were given at regular intervals of 3 or 4 months. Histories of exposures were requested and investigated. During a period of 5 years there have accumulated 272 children who received the total dosage of pertussis vaccine and 256 non-injected have been followed as controls. Among the injected children, there have been reported 42 definite

exposures and 7 clinical attacks. Among the control group, there have been reported 71 definite exposures and 62 cases. By chance, the control group have been exposed to a somewhat greater degree than the injected group, but the difference in attack rates (2.5% for the injected as compared with 24.2% for the control group) is such as to suggest strongly that the procedure had conferred a considerable resistance against infection.

Silverthorne and Fraser[25] reported, in 1938, upon a study which has been in progress at the Hospital for Sick Children in Toronto. Children have been inoculated at the hospital's county branch over a period of 5 years; other children at the county branch, who for some reason were not suitable for vaccination, have been selected and followed as controls. They have been under observation over variable periods of time by public health nurses, or reported upon by a group of physicians in private practice. Among 161 control children there have been 27 "direct" contacts and 23 of these developed whooping cough. In the vaccinated group of 747 children there have been 41 instances of "direct" contact and 2 cases of whooping cough have developed.

Admitting the variable definition of the word "control" in these several studies, the uncertainty surrounding the distribution of exposures and detection of clinical attacks, and the rôle which chance or selection may play in the comparisons, the evidence from the repeated trials points very strongly in one direction, with the exception of the Cleveland experience. The question naturally arises whether in this study the vaccine used differed in some important detail from those used in the others.

Differences in the Vaccines. All used the same method of injection and approximately the same dosage. The vaccines were made from several freshly isolated Phase 1 strains grown for 72 hours on Bordet-Gengou medium, with some differences as to blood content. The bacteria were chemically killed with merthiolate or phenol. The single detail in which there was apparently a significant difference was in regard to the method of suspending the organisms. Sauer, Miller, Singer-Brooks, and Silverthorne scraped the growth off with physiologic salt solution and standardized without washing. Kendrick and Eldering washed off the growth in normal saline, filtered through a thin layer of cotton, centrifuged, discarded the supernatant fluid and resuspended the organisms in saline. Doull, Shibley and McClelland incubated for 48 hours, scraped off the colonies, washed once in sterile distilled water, and resuspended in 0.85% sodium chloride. It is possible, though not proved, that this procedure resulted in a vaccine suspension which was poor in the effective antigenic substance which is peculiar to Phase 1 pertussis bacilli. This substance has not yet been clearly identified, nor are the conditions of its production understood. Further studies of the biology of the organism in this regard are needed.

The method of production of pertussis vaccine is largely empiric and accordingly subject to variation. Until there is a satisfactory laboratory method for assay of immunizing value, there probably will be a considerable difference in the vaccines commercially produced.

Since variation in the amount of effective antigen in a vaccine cannot yet be controlled, attempts to fix the dosage by human trial are subject to imponderable error. The same consideration interferes in attempts

to determine the earliest age at which vaccines can be given, the duration of the resistance conferred, and the necessity for repeating the antigenic stimulus at intervals. Conclusions on these points are premature in the light of evidence at present available.

Summary. Since 1931 additional observations have been accumulated which establish the rôle of *H. pertussis* as a primary incitant of whooping cough. After recovery from human sources the organism tends to undergo regressive changes from a smooth to a rough phase when subcultured on artificial media. Concomitant with this is a gradual loss in immunizing properties. It has been learned empirically by trial on children that an effective vaccine can be made from freshly isolated strains possessing the characteristics of the smooth (Phase 1) variant. The degree of resistance conferred is variable. The studies available do not permit an exact quantitative statement, but range in estimate from very little (Cleveland experience) to almost complete (Evanston) protection. Since the method of injection and the total dosage employed was approximately the same in all the studies, it is inferred that the variability may in part be due to difference in the detail of preparing the antigenic suspension. The effective antigenic substance peculiar to Phase 1 has not yet been definitely identified. The conditions under which maximum yield may be obtained are unknown. Until these have been clarified, only vaccines made and used with strict adherence to the principles set forth above can be expected to confer a considerable degree of resistance. The procedure seems to be relatively free from objectionable reaction. Although severe reactions are occasionally observed, especially in young infants, these are no more so than would be expected with equivalent amounts of any bacterial supension.

KENNETH F. MAXCY, M.D.

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PHYSIOLOGY

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The Effect of the Insulin Shock Treatment for Schizophrenia on Glucose Tolerance. JOHN W. APPEL and JOSEPH HUGHES (Laboratory of the Pennsylvania Hospital, Department for Mental and Nervous Diseases). Sixty-two glucose tolerance tests were performed on 30 patients receiving insulin treatment for dementia præcox. In this treatment, daily injections were given over a period of 2 months, the daily dose ranging from 50 to 200 units of insulin; the average total insulin dosage was 4000 units. All glucose tolerance curves obtained were within normal limits. High curves developed during the treatment. Maximum rises as high as 230 mg. per 100 cc. venous blood were obtained. This maximum rise usually occurred ½ to 1 hour after the ingestion of glucose. All curves, however, had returned to below 115 mg. per 100 cc. by 3 hours. There were 2 exceptions to this. In 7 cases a curve was obtained before and after insulin treatment, and in each of these cases the curve after treatment showed a greater maximum rise than the curve before treatment. No curve failed to show this rise during the course of treatment. In 11 cases a high curve was observed following treatment which thereafter fell to lower levels. In but a single case the curve was found to be not elevated shortly after treatment and showed no significant change at subsequent observations. Most curves had fallen to the pre-insulin level by 3 months. No low curves characteristic of increased tolerance were obtained. A possible basis of these findings could be a temporary inhibition of the secretion of insulin by the pancreas as a result of insulin treatment.

The Fundamental Effects of the Camphor Group. WERNER L. LIPSCHITZ (Laboratory of Pharmacology, University of Istanbul). The mechanism of the action of camphor (borneol, menthon, hexton) was investigated using other tissues than the heart: uterus, intestine, arteries, bronchial muscle. The excised rabbit intestine, when exhausted by 4 hours' work, can be stimulated by camphor. When effective or subthreshold concentrations of camphor were combined with other stimulant or depressant drugs, merely additive effects were observed. On respiring erythrocytes it was found that the curve which plots the degree of effect against the camphor concentration is a biphasic one: by low concentrations the rate of respiration is increased, by higher concentrations it is depressed. If the camphor is removed by repeated washings with saline, the depressant effect not only disappears but the respiration of the stimulated, and even of the previously narcotized, cells is increased above the normal rate (carbohydrate oxidation). The camphor stimulation outlasts the presence of the drug. It pro-

duces a new state of the cell, altering the hydrophil catalytic cell structure. This selective camphor stimulation was found on erythrocytes of the normal, or repeatedly bled, goose and of the rabbit, and on surviving liver slices. It was not found on the non-living (hydrophobe) Warburg model of the respiration (charcoal + oxalic acid). On respiring erythrocytes the same three phenomena of camphor action appear as on the surviving heart: the depression useful in the case of supernormal function, the stimulation useful in cases of deteriorated function, and the persistence of the augmentory action—"Nachbesserung."

Further Studies on the Ballistocardiograph (An Apparatus for the Recording of the Heart's Recoil and the Blood's Impacts in Man). Isaac Starr (Hartzell Department of Therapeutic Research, University of Pennsylvania). Further studies have been made on the ballistocardiograph as a mechanical instrument. Due to vibration periods existing in the human body the descending part of the ballistic curve is an unreliable index of the forces applied. The ascending part is reasonably reliable but it should be corrected for overshooting if the waves are in phase with the body's period.

Abnormal types of ballistocardiogram encountered in patients with heart disease may be derived theoretically from abnormal curves of blood velocity in the aorta. Curves of similar abnormal types have been produced in acute animal experiments by asphyxia, by chloroform and by injuring the right ventricular wall.

When the ballistocardiogram has an abnormal form the formula which permits calculation of cardiac output from the normal record may not be employed. However, new contants for the old formula may be derived theoretically.

The old equation may be written in the following form:

(Cardiac output)^2 = K (altitude of most conspicuous up wave + altitude of most conspicuous down wave in mm.) (aortic cross-section area in cm.^{2}) (duration of cardiac cycle in sec.) (duration of ejection in sec.).

When the form is normal K = 370. For various extremely abnormal forms K has been calculated to range from 690 to 800. For intermediate forms, intermediate values should be taken.

As abnormal forms of ballistocardiogram occur infrequently, except in very sick persons, the opportunity of comparing the cardiac output calculated from the abnormal ballistocardiogram with that obtained by other methods has come infrequently. In 3 cases there was reasonable agreement with results obtained by ethyl iodide.

The Effect of Variations in the Electrolytic and Water Composition of the Body on Anaphylaxis in Guinea Pigs. Mitchell I. Rubin and Milton Rapoport (Children's Hospital of Philadelphia and the Department of Pediatrics, University of Pennsylvania). Male guinea pigs weighing about 250 gm. were passively sensitized to horse serum. The first part of the experiment was concerned with attempts to reduce the severity of the anaphylactic shock. In this group of animals a

dose of serum was used which resulted in death from anaphylaxis in 22 of 25 control animals.

I. In a group of 20 animals depleted of sodium chloride (with no dehydration) by the technique of Darrow and Yannet, the mortality from anaphylactic shock was significantly reduced; only 4 of the 20 animals died. This reduction in mortality is comparable to that obtained in a previous study, where animals were dehydrated by water restriction prior to the administration of the shocking dose of horse serum.

II. In a group of 24 animals given 0.8 to 1 cc. of isotonic potassium chloride intravenously prior to the shocking dose, 13 of the animals survived (a significant figure).

III. A group of 20 animals given magnesium chloride intravenously or magnesium sulphate subcutaneously was protected to a significant degree; 13 of the animals survived. In the survivors, complete muscular relaxation was obtained; in the other animals, no relaxation was apparent prior to the injection of the shocking dose of antigen.

The second part of the experiment involved the exaggeration of the anaphylactic response. In this experiment, a dose of serum was used which killed but 1 of 20 control guinea pigs. In a group of 20 animals rendered edematous by subcutaneous and intraperitoneal injection of normal saline, there was a significant increase in mortality from anaphylactic shock, 7 of the animals dying.

Correction: In the article by Levy, Bruenn and Russell (February issue, p. 244), Dr. Levy requests us to note that under the caption "Normal" (third paragraph) the first sentence should read: "Partial or complete reversal of the direction of *T* in Lead I, in the absence of any *RS-T* displacement in this lead, is of uncertain significance. It was observed in 2 of 66 supposedly normal persons." It should also be noted that in Figure 5, the December, 1937, record should precede instead of follow that of February, 1938.

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